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THE PITUITARY AND ADRENAL CORTEX IN GENERAL MEDICINE*

BY

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The rapid progress of medical research is leading inevitably to increasing specialization in ever-narrowing fields. Endocrinology is no exception, but at the same time it has become apparent that the hormones of the adrenal cortex and anterior pituitary gland are concerned in many medical and surgical conditions that are not primarily endocrine in origin.

In these lectures it is intended to review the role of the adrenal cortex in the response to stress, to discuss the importance of secondary aldosteronism in the production of oedema, to consider the non-endocrine indications for total adrenalectomy, and, finally, to discuss the pharmacology and dangers of high-dosage steroid therapy with cortisone and its newer synthetic derivatives.

The hormones of the anterior pituitary gland are complex polypeptides and it is proving difficult to isolate, purify, or estimate them. Progress in this field has been less spectacular than in the case of the adrenal cortical hormones, but there is evidence that growth hormone has some action in non-endocrine conditions.

Hormones of the Adrenal Cortex

The main hormones secreted by the adrenal cortex are shown in Fig. 1. Those on the left are produced under the influence of corticotrophin; aldosterone excretion continues in the absence of this pituitary

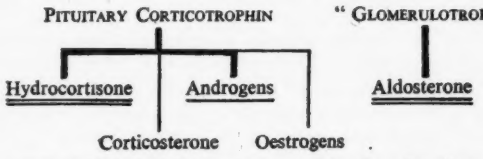

FIG. 1.—Principal hormones secreted by the adrenal cortex.

hormone. From the point of view of maintenance of life the two important hormones are hydrocortisone and aldosterone. Corticosterone is produced in comparatively small amounts, though it is of much greater significance in some animals (Bush, 1953). The adrenal secretes small quantities of oestrogens, and this may be important in women with breast cancer, or after the menopause or oophorectomy (Bulbrook *et al.*, 1958). Cortisone is not produced to any great extent by the adrenal, but there is considerable interconversion of hydrocortisone and cortisone in the body (Gold *et al.*, 1959) and their actions are essentially similar.

*The first part of the Oliver-Sharpey Lectures delivered at the Royal College of Physicians of London on March 8 and 10, 1960.

Hydrocortisone and cortisone are often referred to as glucocorticoid hormones because by promoting gluconeogenesis and by reducing carbohydrate utilization they tend to raise the blood sugar. This is unfortunate because these hormones normally have only a minor role in the regulation of carbohydrate metabolism. Their most important actions are concerned with the distribution of water and sodium between the various fluid compartments of the body, and the maintenance of blood-pressure and renal function. These actions can be demonstrated by studying the changes produced by cortisone withdrawal in salt-loaded adrenalectomized patients. Fig. 2 shows the results of an investigation of this type undertaken in 1957 with the help of Drs. G. Walker and M. M. Martin.

The patient was normally controlled on 12.5 mg. of cortisone six-hourly; this was discontinued for a period of 72 hours and then 50 mg. of hydrocortisone (cortisol) was given intravenously. Sodium intake was 200 mEq/day and positive balance was maintained; the cumulative sodium balance and total exchangeable sodium were parallel, the latter being measured with ^{22}Na and an external body counter (Martin and Walker, 1957). In the second part of Fig. 2 it will be seen that there was little change of body weight, an increase of total body water (antipyrine), and a reduction of inulin space. The glomerular filtration rate (G.F.R.) fell, but this was corrected by intravenous hydrocortisone. The loss of diurnal rhythm of water excretion is also shown. Similar studies have been reported by Hills *et al.* (1953) and Mendelsohn and Pearson (1955). The former noted reduction of inulin space and increase of total body water, whereas Mendelsohn and Pearson reported that the inulin space increased without any change of total body water.

The essential physiological actions of hydrocortisone and cortisone may therefore be summarized as: (*a*) maintenance of distribution of water and sodium between the cellular and extracellular fluids; (*b*) maintenance of blood-pressure; (*c*) maintenance of G.F.R.; and (*d*) necessary for renal excretion of water.

Aldosterone has little action in these spheres in the amounts present in the circulation. It is concerned principally with sodium and potassium homoeostasis, and exerts its effect through the renal tubule. At the same time it has some action on the sodium/potassium ratio of the saliva, sweat, and faeces (Thorn *et al.*, 1955).

There are two vital adrenal cortical hormones with different actions; it is therefore not surprising that two types of acute adrenal insufficiency can be differentiated (Lipsett and Pearson, 1956). In one there is an absolute

or relative lack of hydrocortisone, resulting from true deficiency or increased demand and exemplified by the patient just described, from whom cortisone was temporarily withdrawn. The second is due to lack of aldosterone, leading to sodium depletion, hypotension, and extrarenal uraemia with marked elevation of plasma potassium. This type of crisis is seen in some adrenalectomized patients treated with cortisone alone and in whom the sodium intake is inadequate: it comes on rather more slowly than the crisis of acute hydrocortisone deficiency. Differentiation between these two types of acute adrenal insufficiency is important because they do not respond to the same treatment. The hydrocortisone-deficient type responds well to intravenous hydrocortisone, and the sodium-deficiency type to intravenous saline with sodium-retaining hormone. The classical crisis of untreated Addison's disease is a combination of the two and needs treatment with hydrocortisone, intravenous saline, and sodium-retaining steroid.

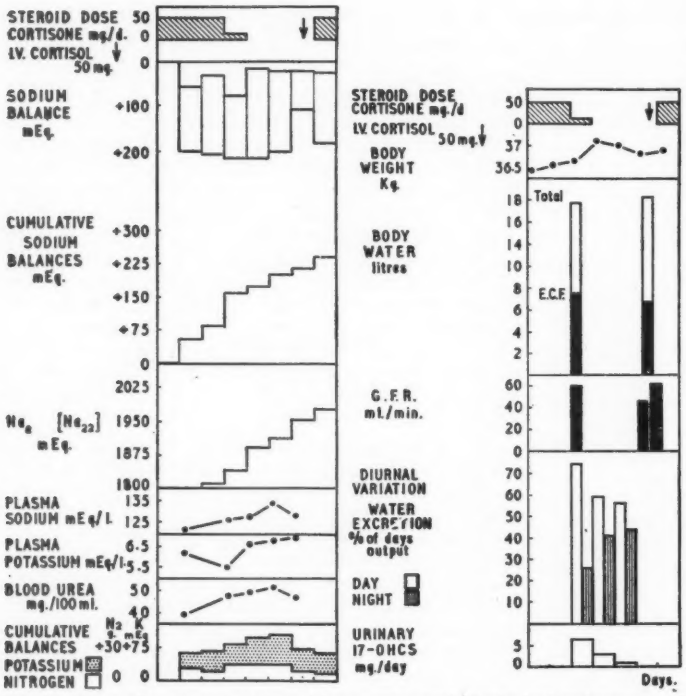

FIG. 2.—Effect of cortisone withdrawal in a woman aged 48 who had undergone total adrenalectomy for widespread metastatic carcinoma of the breast.

The Adrenal and Stress

It is well recognized that patients with Addison's disease respond badly to the stress of an acute illness or infection or to a surgical operation. In these conditions the maintenance of blood-pressure, fluid distribution, and renal function require higher levels of circulating hydrocortisone than in the normal resting state. A considerable amount of work has been done to try to assess the types of stress that lead to increased hydrocortisone production. Thorn subjected a number of normal individuals to stressful situations and found that exposure in a cold room, anoxia, and emotional upsets were without effect on the urinary steroid excretion; the only clear responses were with boat-race crews, and the cox and coach were affected as much as the actual crew (Thorn *et al.*, 1953). The plasma level of hydrocortisone may be raised by emotional stress (Mason, 1959) or by taking amphetamine sulphate (Bayliss, 1955). Emotional factors may also result in increased aldosterone production (Venning *et al.*, 1957).

Serious illnesses like coronary thrombosis (Bayliss, 1955), cerebrovascular accidents (Oka, 1956), and fulminating infections (Melby and Spink, 1958) cause increased adrenal production of hydrocortisone. Pain and shock are probably the two main factors responsible (LeFemine *et al.*, 1957). Tyler *et al.* (1953) have pointed out that to cause a marked elevation of the plasma hydrocortisone level it must be a "life-threatening" type of stress. They reported a patient in severe diabetic ketosis with a level of 51 μg./100 ml., falling to 8 μg./100 ml. three weeks later (Perkoff *et al.*, 1954). Patients who are dying (Sandberg *et al.*, 1956) and those in peripheral circulatory failure due to fulminating infections (Melby and Spink, 1958) have been found to have very high plasma levels. In these cases not only is there evidence of increased hydrocortisone production by the adrenal, but also the rate of hepatic conversion of free hydrocortisone to its inactive metabolites is reduced. It seems clear that in severe illness there is an increase of hydrocortisone production and that if it fails, or sometimes despite its occurrence, there may be severe hypotension and peripheral circulatory failure. The significance of these findings in patients with severe illnesses cannot yet be assessed. It is possible that if the level of circulating hydrocortisone were raised still higher in some of these shocked patients the circulatory status would be improved. This means higher than a normal adrenal can achieve, and may be evidence in favour of giving intravenous hydrocortisone to shocked patients without invoking adrenal exhaustion or failure (DiRaimondo and Forsham, 1958).

There has been considerable interest in the last few years in the metabolic response to stress and the possible role of the adrenal cortex in the changes in electrolyte and nitrogen excretion. It is difficult to investigate this relationship in medical stress. Studies have been reported in which the metabolic and steroid changes after corticotrophin have been compared with those resulting from artificial fever produced by intravenous typhoid vaccine and other pyrogens; the results were inconsistent, and the metabolic changes could not be correlated with altered adrenal cortical activity (Conn *et al.*, 1954). Most of the studies of the metabolic response to stress have been made in surgical patients. It has been shown that the hydrocortisone level in the plasma may be raised before operation if there is anxiety (Frankssson and Gemzell, 1955), and that a further rise follows induction of anaesthesia, especially if ether or cyclopropane is used (Hammond *et al.*, 1958). The very considerable increase during and shortly after the operation is due partly to increased adrenal cortical production

and partly to reduction of the rate of metabolism of the steroid by the liver (Tyler *et al.*, 1954), although studies with hydrocortisone infusion in the immediate post-operative period have given conflicting results (Murray *et al.*, 1958 ; Dudley *et al.*, 1959).

Aldosterone excretion is often increased after operation (Llaurado *et al.*, 1956). This increase correlates poorly with changes in urinary sodium output (Venning *et al.*, 1958), and sodium retention can occur after operations on adrenalectomized patients (Forrest *et al.*, 1957) and Addisonians (Randall and Papper, 1958). Indirect evidence was given some years ago that post-operative sodium retention is the result of sodium deficiency (Flear and Clarke, 1955). More recently Hayes *et al.* (1959) have studied the problem and shown that the post-operative increase of urinary aldosterone is not an essential part of the metabolic response to surgery but the result of sodium depletion possibly from local immobilization of extracellular fluid at the operation site.

Metabolic Response to Surgery

The chief features that make up the metabolic response to surgery are an initial antidiuresis, a rather longer retention of sodium and chloride, and negative balances of potassium and nitrogen. In considering the possible causes of these changes there are the relative or absolute starvation that accompanies the operation, the increased production or circulating level of adrenal cortical hormones, and the effects of the operation itself —tissue damage, loss of blood, and local oedema. Attempts have been made, by keeping the adrenal steroid level and electrolyte intake constant, to eliminate these factors and ascertain the metabolic changes due to the stress itself (Mason, 1955 ; Robson *et al.*, 1955 ; Jepson *et al.*, 1957).

To keep the steroid level constant intramuscular cortisone in adequate, but not excessive, doses should be started 10–14 days before the operation. This will ensure a constant level of urinary excretion (Sprague *et al.* (1950) but cannot compensate for any alteration in the rate of hepatic metabolism or for possible changes of steroid binding by plasma proteins which may reduce physiological activity (Sandberg *et al.*, 1957). The food intake must be kept absolutely constant if this factor is to be eliminated ; it has been demonstrated that alterations of potassium and nitrogen intake may influence the sodium balance in the post-operative period (Krieger *et al.*, 1958). Between 1955 and 1957, with the help of Dr. G. Walker, a number of studies of this type were made. Most of the patients were undergoing total adrenalectomy under the care of Mr. D. H. Patey and Mr. L. P. LeQuesne. Steroid levels were kept constant by giving intramuscular cortisone (100 mg. daily), starting 10–14 days before operation. Food intake was kept constant by giving a slow intragastric drip of an emulsified feed of identical composition with the diet ; this was started a few hours after the end of the operation.

Cumulative balance figures showed that the metabolic response to surgery was reduced if steroid levels and food intake were kept constant. There was, however, reduction of urinary sodium and increased nitrogen excretion after operation. Potassium losses were much reduced if adequate intake was maintained. The results were similar to those of Abbott *et al.* (1959). There is general agreement that the overall pattern of the metabolic response to stress still occurs when the steroid level is kept constant, but that the level required is much higher than normal. It has been demonstrated in adrenalectomized animals that the response does not occur in the absence of adrenal steroids (Ingle *et al.*, 1947). There is little evidence that the magnitude of the metabolic response is related to the degree of adrenal hyperfunction, although in studies of severe diabetic ketosis it has been shown that the negative nitrogen balance bears some relation to the 17-hydroxysteroid excretion (Nabarro *et al.*, 1952).

Aldosterone and Oedema

Chemists and clinicians studying the role of aldosterone in oedema are all agreed that the problems involved in measuring aldosterone production and excretion are considerable. Much of the early work done in this field can be criticized on grounds of unreliable methodology. Aldosterone production by the adrenal cortex amounts to about 0.2 mg./day in a normal subject and the level in the blood is very low. Little free aldosterone is present in the urine, but a measurable amount is excreted as an unusual conjugate hydrolysed by acid at room temperature, and there are also metabolites conjugated with glucuronic acid. There is no specific reaction for aldosterone ; it can only be estimated by physical or chemical reactions that are also given by the very much larger quantities of hydrocortisone and other steroids present in the urine. Measurement of urinary aldosterone therefore involves several chromatographic purification procedures to free it from other steroids before the final estimation can be performed (Ayres *et al.*, 1957b). An important step forward is the use of tritium-labelled aldosterone. If this is injected into the patient and the urine collected over the next 24 hours a figure can be obtained for the rate of aldosterone secretion by the adrenal gland (Ayres *et al.*, 1957a).

Most of the methods used for aldosterone estimation depend on separation of the aldosterone from the urine after hydrolysis at *p*H 1. If this figure is to be of value it must represent a consistent proportion of the aldosterone produced each day by the adrenal. When tritiated aldosterone is given to the patient to measure the secretion rate, it is possible to determine the proportion of radioactivity secreted in the free state, as the acid hydrolysed conjugate and as glucuronide (Jones *et al.*, 1959 ; Peterson, 1959). This is shown diagrammatically in Fig. 3. Repeated estimations of secretion rates and distribution of urinary radioactivity in two patients have suggested that the urinary *p*H 1 extractable aldosterone may vary much more than the actual secretion rate (Hurter and Nabarro, 1960). Results

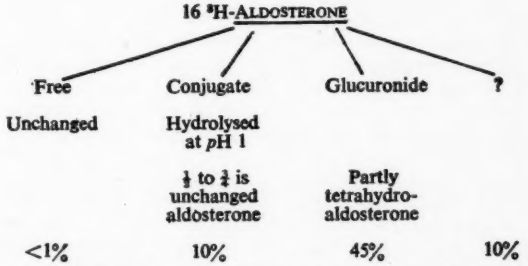

FIG. 3.—Distribution of radioactivity in a 24-hour collection of urine after injection of 1 μg. of tritiated aldosterone.

TABLE I.—*Urinary Excretion of Radioactivity in a 24-Hour Period After Intravenous Administration of 1 μg. of 16 ^{3}H-aldosterone. Four Estimations on a Patient with Congestive Cardiac Failure*

Date	Secretion Rate μg. 24 hrs.	Percentage of Radioactivity	
		In *p*H 1 Hydrolysate	As Glucuronide
August 8 ..	1,430	6·3	17·3
,, 12 ..	1,560	6·0	20·4
,, 16 ..	940	10·6	30·2
,, 20 ..	1,340	14·7	20·7

of four determinations in a patient with cardiac failure are shown in Table 1.

The control of aldosterone secretion in experimental animals and normal subjects has been clarified considerably in recent years by the work of Bartter and his group, and by Farrell. Farrell (1959) has obtained evidence that aldosterone secretion is controlled by a tropic hormone, "glomerulotropin," released from an area of the posterior diencephalon and pineal body. Bartter *et al.* (1959) have studied the various factors that influence aldosterone secretion. These include reduction of the intravascular volume in certain parts of the body and, to a less extent, potassium levels and corticotrophin. The intravascular volume operates in two areas; reduction of flow through the carotid artery stimulates increased production of aldosterone; removal of the arterial constriction does not necessarily allow aldosterone production to return to normal—there is a separate "turning off" mechanism. This has been located in the right auricle, distension of which tends to lower aldosterone secretion. These centres operate via the sinus and vagus nerves respectively.

Even before aldosterone had been isolated, potent salt-retaining substances had been detected in the urine of patients with the nephrotic syndrome (Deming and Luetscher, 1950). This has been shown to be aldosterone (Luetscher *et al.*, 1954), and an excess of aldosterone has also been found in patients with cirrhosis with ascites and oedema (Dyrenfurth *et al.*, 1957), cardiac failure (Luetscher *et al.*, 1956), episodic oedema (Luetscher and Lieberman, 1958), and oedema due to increased capillary permeability (Thorn *et al.*, 1957). In these cases it is important to consider what part the increased secretion of aldosterone plays in the production or maintenance of the oedema. Experimental administration of large amounts of aldosterone does not produce oedema in a normal subject; after a period of retention of sodium and water an "escape" from the aldosterone effect is seen and the patient comes back into sodium balance (August and Nelson, 1959). In patients with secondary hyperaldosteronism there must be some factor at work interfering with the escape phenomenon.

Muller (1959) has reviewed some of the factors involved in oedema production in uncomplicated nephrosis in children and in congestive cardiac failure. He has suggested that in nephrotic children lowered plasma osmotic pressure allows escape of oedema fluid from the capillaries, and this in turn reduces plasma volume. The carotid mechanism of aldosterone regulation is stimulated and significant overproduction results. The sodium that is retained, however, does not remain in the circulation but escapes through the capillaries, and hence the stimulus to increased aldosterone production persists. In cardiac failure the secretion rates of aldosterone are not nearly so high as in nephrosis, and Muller has suggested that there is failure of the "turning off" mechanism. Until there is more detailed information available about the site of origin of the right-auricular impulses it is not possible to evaluate this hypothesis.

Aldosterone levels of oedematous patients vary with the salt intake, but an oedematous patient does not reduce aldosterone excretion in response to a salt load nearly as well as a non-oedematous subject (Duncan *et al.*, 1956). Diuretics tend to raise the aldosterone levels unless they result in improvement in the cardiac condition, in which case there may be reduction (Muller, 1959). Venesection acts similarly. Removal of the ascitic fluid from a cirrhotic patient results in striking increases of aldosterone levels (Wolff *et al.*, 1958). These studies are interesting but do not clarify the relationship between secondary aldosteronism and oedema.

A more direct approach has been the use of amphenone, a compound which inhibits many enzyme systems of the body including those needed for synthesis of steroids (Hertz *et al.*, 1956). The effect of giving amphenone and inhibiting aldosterone synthesis in patients with oedema has been investigated in a number of centres, and the results of some of these studies are shown in Table II. It is clear from these

TABLE II.—*Effect of Amphenone on Sodium Excretion in Patients with Secondary Hyperaldosteronism*

Underlying Condition	Urinary Aldosterone before Amphenone (μg./Day)	Urinary Sodium (mEq/Day)		
		Before Amphenone	On Amphenone	
C.C.F. ..	10	5	10	Muller (1959)
	14	5	70	
	33	<1	3	Thorn *et al.* (1957)
	74	5	5	Hill *et al.* (1959)
Nephrosis ..	23	1	20	Lieberman (1958)
Cirrhosis ..	43	1	105	Stormont *et al.* (1959)
	43	1	1	
	26	5	13	
Abnormal capillary permeability	89	1	28	Renold *et al.* (1957)

results that stopping the secretion of aldosterone in oedematous patients does not necessarily result in a diuresis. Recent studies have shown that an analogue of amphenone, 2-methyl-1,2 bis-(3-pyridyl)-1-propanone (SU 4885), also interferes with aldosterone synthesis and gives similar results (Coppage *et al.*, 1959).

Another approach to the problem is to use the newly developed spirolactone series of compounds. They have little effect on sodium and potassium excretion in adrenalectomized dogs in the absence of sodium-retaining steroids; they will, however, block the action of aldosterone on the renal tubules (Slater *et al.*, 1959b). In intact humans it has been shown that 1 mg. of spirolactone (SC 8109) will partially neutralize the action of 0.5 μg. of aldosterone (Ross and Bethune, 1959). In an adrenalectomized dog given the 7α-thioacetoxy derivative (SC 9420) by mouth and a continuous infusion of aldosterone intravenously we have shown that 30 mg. of spirolactone will partially inhibit the action of 21.5 μg. of aldosterone. The inhibition starts about two hours after the spirolactone is given and continues for more than eight hours. 50 mg. given by mouth completely inhibits the action of 5 μg. of aldosterone given as a single intravenous injection.

In practice the responses to these compounds are variable. Fig. 4 A shows an excellent response in a

patient with cirrhosis, ascites, and oedema. His aldosterone secretion rate at this time was 205 μg./day, very low for a patient on a low-sodium diet. Studied later after a haematemesis, at a time when his aldosterone secretion rate exceeded 1 mg./day, the response to spirolactone alone was disappointing. The additive effects of chlorothiazide, spirolactone, and mersalyl are shown in Fig. 4 B. Subsequently, prolonged administration of spirolactone had little effect on sodium output, although there was a fall of the urinary excretion of *p*H 1 extractable aldosterone (Fig. 4 C). The mechanism of this is unexplained; we have noted it previously in patients responding poorly to spirolactone. In this case it was not accompanied by a corresponding fall of the aldosterone secretion rate. Our results in this and other patients suggest that when the aldosterone levels are very high the response to spirolactone alone is likely to be disappointing. This may be because the amount of spirolactone given has been inadequate. Alternatively, it may be that when the aldosterone levels are very high they play a comparatively small part in the oedema, and that, when they are lower, inhibiting just this one factor in sodium retention allows a diuresis to occur.

There are unexplained differences between primary and secondary hyperaldosteronism. Oedema is very common in the secondary variety but unusual in Conn's syndrome; on the other hand, potassium depletion and hypokalaemic muscular paralysis are often features of primary aldosteronism but rare in the secondary type. In a normal subject aldosterone causes initial sodium retention followed by an "escape" and return to sodium balance (August and Nelson, 1959). The aldosterone causes expansion of the extracellular fluid, increase of plasma volume, and elevation of the glomerular filtration rate. This results in increased sodium excretion, but it may not be the only factor in the escape phenomenon (Relman *et al.*, 1958). Admittedly patients with Conn's syndrome often have a low G.F.R., but there is a considerable fall after operation followed by a gradual rise (Hewlett *et al.*, 1957; Milne *et al.*, 1957). The low G.F.R. before operation may be due to potassium depletion (Schwartz, 1955). In secondary hyperaldosteronism sodium retention does not expand the plasma volume, because the sodium retained leaks out into the tissues and aggravates the oedema. The absence of potassium depletion in the secondary variety has been attributed to the very small amounts of sodium in the distal renal tubules and hence inability to exchange potassium for sodium. Patients given salt-retaining steroids do not have a potassium diuresis if they are on low-sodium diets (Relman and Schwartz, 1952). An additional factor may be that patients with Conn's syndrome rarely have adenomata producing exclusively aldosterone (Lieberman *et al.*, 1958), and the combination of aldosterone with other steroids like corticosterone may increase the potassium loss (Ross, 1960).

TABLE III.—*Indications for Total Adrenalectomy*

Cushing's syndrome (adrenal cortical hyperplasia)	Removes source of excess hydrocortisone
Carcinoma of breast	Removes source of oestrogens
,, ,, prostate	Removes source of androgens
Cirrhosis with ascites	Removes source of aldosterone
Intractable oedema	
Malignant hypertension	? Removes source of aldosterone
Diabetes with complications	?

The commonest indication for the performance of this operation is disseminated cancer of the breast. Reports of long-term follow-up have been published by Dao and Huggins (1957) from Chicago, and from the Sloane Kettering Cancer Research Institute in New York (Fracchia *et al.*, 1959). A large series of cases have been described in this country by Stanford Cade (1957). Remissions are obtained in about 40% of cases and may last as long as five years. The most promising cases are those with multiple bony metastases appearing several years after the treatment of the primary tumour. Cases with liver involvement usually fail to respond. Because only 40% of patients respond, attempts have been made to devise effective methods for the selection of suitable cases. The operation is indicated in patients with tumours stimulated by oestrogens, and, if the history shows that the patient has had a good response to oophorectomy, response to adrenalectomy may also be anticipated. It is more difficult to assess the response to irradiation of the ovaries or administration of androgenic hormones. Emerson and Jessiman (1956) have suggested stimulation and suppression tests using oestrogens and cortisone. These tests are difficult to apply, and it is generally necessary to rely on a clinical assessment.

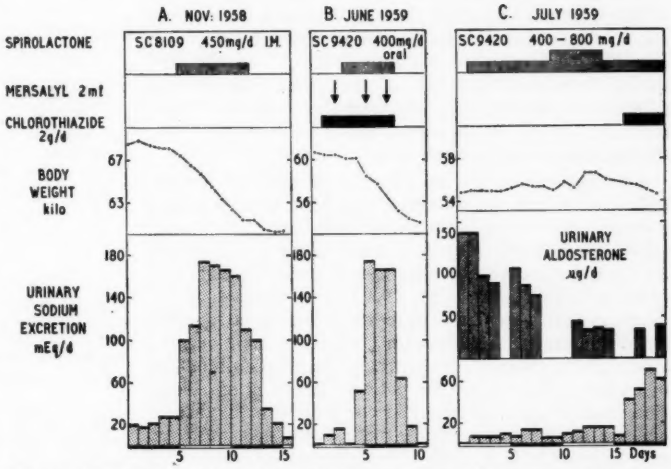

FIG. 4.—Man aged 63 with cirrhosis of the liver, ascites, and oedema. *A*, November, 1958. Aldosterone secretion rate 205 μg./day, good response to spirolactone (SC 8109) intramuscularly. *B*, June, 1959. Aldosterone secretion rate >1,000 μg./day, effect of spirolactone (SC 9420), 400 mg./day by mouth, with chlorothiazide and mersalyl. *C*, July, 1959. Effect of prolonged administration of spirolactone.

The results of total adrenalectomy for malignant hypertension were reported by Thorn *et al.* (1952). There was often improvement in the appearance of the optic fundi, but to lower the blood-pressure it was necessary to keep these patients on the fringe of adrenal insufficiency, renal function was often further impaired, and the plasma potassium tended to rise rather alarmingly. To control this it was necessary to give additional salt-retaining steroid, and the blood-pressure went up

Total Adrenalectomy in Non-endocrine Conditions

Total adrenalectomy has been undertaken in a number of non-endocrine conditions (Table III).

again (Morse *et al.*, 1959). Another group of cases have been followed in Philadelphia, but here the adrenalectomy was usually subtotal and often combined with sympathectomy (Jeffers *et al.*, 1953). Three groups of cases have been reported in this country; the effect of the operation on the blood-pressure has usually been disappointing, but there was no doubt that the papilloedema and appearance of the optic fundi improved (Arnott *et al.*, 1957; Hanley, 1957; van't Hoff, 1957). The operation carries an appreciable mortality, the difficulties of post-operative care are considerable, and with improvement of hypotensive drugs its performance can seldom be indicated for hypertension.

The rationale for undertaking total adrenalectomy for diabetes with retinitis and vascular disease is not entirely clear. Two series of cases have been reported (Wortham and Headstream, 1954; Malins, 1956). In the first series, three died and two of the other four showed slight improvement. In the second there was one death, one case showed improvement in the retinitis, and four showed no change or were worse.

Adrenalectomy may be effective in cases of intractable fluid retention. Good results have been reported in cases of cirrhosis of the liver with ascites (Marson, 1954; Giuseffi *et al.*, 1957; Baronofsky *et al.*, 1960). and in a patient with oedema due to abnormal capillary permeability (Thorn *et al.*, 1957). A number of the diabetics with vascular disease and proteinuria reported by Wortham and Headstream (1954) lost their oedema after adrenalectomy. In hypertensive heart failure loss of oedema may benefit the patient (Thorn *et al.*, 1952). The effect of adrenalectomy in one patient with episodic oedema has been described—the oedema was improved but the patient's underlying psychological difficulties remained (Thorn *et al.*, 1956). In these cases it would seem that aldosterone removal is the operative mechanism, and if the spirolactone group of aldosterone-blocking drugs prove effective, surgery will not be necessary.

We have made observations on operative cover and post-operative replacement therapy on 68 patients undergoing total adrenalectomy. Seven of these were for Cushing's syndrome and 61 for non-endocrine conditions (carcinoma of breast 56, prostate 3, hypertension 2). The steroid cover that we are at present using when the operation is performed for carcinoma is shown in Table IV. The use of intramuscular cortisone in these doses results in excellent sodium conservation in the post-operative period. It is not necessary to give additional salt-retaining steroid or extra salt. Intravenous hydrocortisone has been used to cover the operation in a few cases, but sodium conservation may then be much less effective (Fig. 5) and sodium-retaining steroid should be used. By the sixth day after operation the dose of cortisone is usually down to 12.5 mg. q.d.s.

TABLE IV.—*Steroid Cover for Total Adrenalectomy in Cases of Carcinoma of the Breast or Prostate*

4-days pre-op. ...	Cortisone 100 mg. daily i.m.	
D—Op.	Cortisone 100 m. i.m. pre-op.	I.V. isotonic saline 500 ml.
	Cortisone 50 mg. i.m. 6-hourly post-op.	Subsequently 5% dextrose. Blood if required
D + 1 ..	Cortisone 50 mg. 8-hourly i.m. or oral	
D + 2 ..	Cortisone 50 mg. 8-hourly oral	
D + 3 ..	Cortisone 25 mg. 6-hourly oral	
D + 4 } D + 5 }	Cortisone 25 mg. 8-hourly oral	
D + 6 onwards	Cortisone 12·5 mg. 6-hourly Fludrocortisone 0·1 mg. daily	

Plasma Na and K and blood urea estimated before operation and 10 days after. If the latter is abnormal adjustment of fludrocortisone dose is indicated.

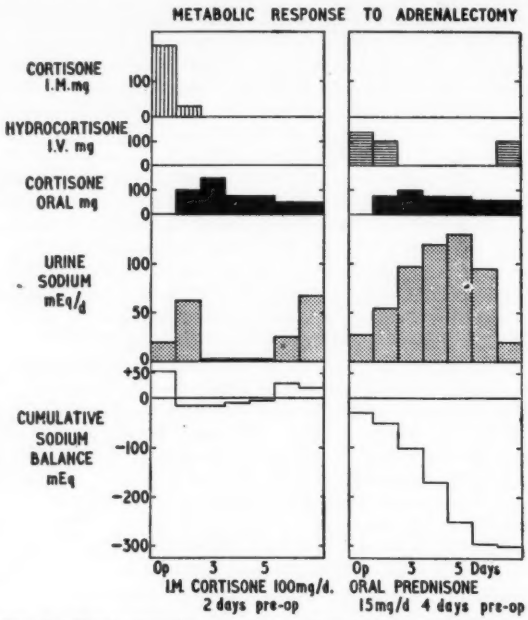

FIG. 5.—Total adrenalectomy for carcinoma of breast. Urinary sodium excretion and cumulative sodium balance. Left: woman aged 51—routine steroid cover with intramuscular and oral cortisone. Right: woman aged 46—steroid cover with intravenous hydrocortisone and oral cortisone.

and the administration of 0.1 mg. of fluorocortisone a day is started (Table IV). We have come to the conclusion that 50 mg. of cortisone a day with extra salt is not always adequate as replacement therapy for the totally adrenalectomized patient. A sodium-depletion type of Addisonian crisis may be produced, and the use of a small dose of fludrocortisone with the cortisone is now recommended as a routine procedure (Nabarro and Walker, 1957).

[*The second part of the Oliver-Sharpey Lectures will appear in next week's issue.*]

"At this point you must allow me a very brief digression on the subject of pastoral diets. As I imagine most of you know, the milk of the camel, as compared with cow's and goat's milk, is deficient in mineral salts, particularly those of calcium. As a result, the physique of the camel man is a very slight one; indeed, compared with the camel-owning desert Somali, the cattle-owning savannah country Masai is a percheron to a racehorse. But not only is the camel man light-boned, he is also extremely excitable and volatile. His temperament can be described in the terms used by Lavater of Fuseli: 'His look is lightning, his word a storm, his jest death, his vengeance Hell—at close quarters he is rather trying.' All this is attributable I suppose to mineral deficiency. A distinguished old man, the head of his clan, who owned large herds of both cattle and camels, once told me that it was a tradition amongst the noble families of his tribe to insist that the young men who were later to take over the leadership of the people should spend their formative years with the cattle rather than with the camels. Understandably, he did not explain the custom in terms of the mineral salt content of various milks or of the assimilation of calcium but just said that he found that the young men raised in this way seemed to have more sense than those who spent their time with the camels." (Speech by Sir Richard Turnbull at opening of Scientific Conference on Malnutrition, Dar es Salaam, 1960. *E. Afr. med. J.*, May, 1960.)

STILBOESTROL, PHENOBARBITONE, AND DIET IN CHRONIC DUODENAL ULCER

A FACTORIAL THERAPEUTIC TRIAL

BY

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During the twentieth century chronic duodenal ulcer has emerged as one of the major diseases of Western society, although there is strong evidence that previously it was comparatively uncommon (Craig, 1948). Its medical treatment is unsatisfactory, as can be judged from the large numbers of patients who are brought to surgery. Surgery is essential for the treatment of certain complications of duodenal ulcer, such as perforation, stenosis, and massive bleeding, but its widespread use in the treatment of uncomplicated ulcer is an indictment of conventional medical treatment.

A chronic peptic ulcer gives rise to periodic bouts of symptoms, usually with complete freedom of pain for weeks or months between them; this periodicity of symptoms is particularly marked in duodenal ulcer. It follows that any treatment which relieves symptoms will at first sight appear to be beneficial, but only long-term studies on a comparative basis will show whether one treatment is more effective than another in healing the ulcer.

The usual course of treatment is based on the principles laid down by Sippy (1915) of attempting to counteract the acidity of the gastric juice by administration of alkalis and by frequent small feeds of a bland diet rich in milk. Alkalis produce rapid though temporary relief of the pain of peptic ulcer, but there is no objective evidence that their administration leads to an increased chance of the ulcer healing. There is little evidence that a bland diet improves the long-term course of chronic peptic ulcer. Recently, anticholinergic drugs have been much used, but the few controlled studies that have been made have shown no favourable long-term results.

Influence of Age and Sex

One of the conspicuous features of duodenal ulcer is its predilection for the adult male. In childhood, chronic peptic ulcer is uncommon and the two sexes are then equally affected (Sandweiss *et al.*, 1939). After puberty its frequency increases, and a heavy male preponderance becomes apparent. From the age of 20 years onwards, duodenal ulcer is common in men. An ulcer causing symptoms is most commonly found in men aged about 45, but this is clearly a complex situation and is a function of the average length of time a chronic ulcer lasts and the chance of developing it at particular ages. It has been shown by Doll and Avery Jones (1951) that the chance of a man developing a duodenal ulcer remains remarkably constant between the ages of 20 and 65. By contrast, the chance of a woman developing a duodenal ulcer remains relatively low throughout the whole of her active reproductive life but increases sharply at the menopause. A good study of this relationship of chronic ulcer to the menopause is that of Clark (1953), who showed that "an unduly large proportion of ulcers start, flare up, or undergo complications at or about the time of the menopause."

Not only is duodenal ulcer much less common in women than in men, but it appears to run a less severe course, at any rate judged by the liability to perforation. It is probably fair to take this complication as a measure of severity, for its occurrence implies that the ulcerating part of the process has gained dominance over the reparative part sufficiently to penetrate the entire thickness of the duodenal wall. The male: female ratio for uncomplicated duodenal ulcer varies from 3:1 to 10:1 in different series, and the ratio might be expected to be similar for perforations. In the Radcliffe Infirmary, during the period 1938–51 which preceded the present study, there were 388 duodenal perforations in men compared with only 20 in women, a ratio of nearly 20:1.

Another feature of duodenal ulcer in women is the protective effect of pregnancy. When a woman with a chronic peptic ulcer becomes pregnant it is usually found that she is symptom-free during pregnancy, although symptoms are likely to recur during the early months after delivery (Clark, 1953). Perforation of a chronic ulcer during pregnancy is uncommon enough to excite comment when it does occur.

Oestrogens and Peptic Ulceration

These peculiarities of peptic ulcer in relation to sex can be interpreted in many different ways, but one possibility is that circulating oestrogens have an anti-ulcer effect. That this might be so has occurred to a number of workers, and some observations have been made both on animals and on human beings. Korbsch (1937) treated four men with gastric ulcer with intramuscular injections of an oestrogen, and obtained such rapid healing of the ulcers that he referred to the results as astounding. Schulz (1940) treated nine ulcer patients with oestrogens and claimed good results. Winkelstein (1936), working with dogs, found that ulceration of the skin occurring in the neighbourhood of a gastric pouch was healed by natural oestrus and that the administration of the oestrogen "theelin" also brought about healing in both a female and a male dog. The gastric secretions were usually not depressed, so that healing was not the result of an inhibition of gastric secretion. Later he used oestrogen therapy in 20 female ulcer patients during the menopause. There was a good symptomatic response, but there were frequent recurrences. The recurrences were also relieved by oestrogen therapy (Winkelstein, 1940).

The action of the synthetic oestrogen stillboestrol was studied by Nasio (1946) in relation to the occurrence of cinchophen ulcers in dogs. Nasio had evolved a technique of administration of cinchophen which would invariably cause peptic ulceration to occur in untreated animals. Stilboestrol prevented the appearance of cinchophen ulcers in 100% of male dogs; it was less effective in bitches, only 22% being protected. He had previously shown that a pituitary extract, "antuitrin S" was ineffective.

From what has already been said about the episodic character of the symptoms of duodenal ulcer it is plain that the clinical observations cited above are of very limited value in judging whether oestrogens assist in

actual healing of a peptic ulcer in man. The animal experiments were concerned with types of ulceration so different from the naturally occurring illness of man that direct transposition of the results would be foolish. Nevertheless, there is sufficient evidence to justify a more formal trial of the action of oestrogens in duodenal ulcer, and especially in men rather than in women.

Objects of the Present Study

The main object of this study was to test the effect of small doses of stilboestrol on the course of duodenal ulcer in men. However, when conducting a therapeutic trial there is no need to confine oneself to testing the effect of one form of therapy. Provided a suitable experimental design is chosen, several different forms of therapy can be tested simultaneously without any loss of precision in measuring the effect of any one of them, for reasons which are set out below. Such a factorial trial represents a great economy of labour, and it was therefore decided to test two conventional forms of therapy in addition to stilboestrol. The first of these was a diet. A Sippy diet, or some modification of it under another name, is still extensively used in peptic-ulcer treatment, although there appears to be no convincing positive evidence of its value. The second conventional agent chosen for test was phenobarbitone. At the time this study began, the view that duodenal ulcer is a psychosomatic disorder was prevalent and sedatives were in wide use. Indeed, a well-known British gastroenterologist had expressed the following opinion: "The most important single drug in the management of peptic ulcer is phenobarbitone, given in sufficient doses to have the desired effect of sedation" (Avery Jones, 1949).

Alkalis and antacids were not used in the present study except for the relief of troublesome pain in those patients who suffered from clinical recurrences. In other words, they were held in reserve to be used when necessary as a form of temporary symptomatic relief, which is probably their sole useful function in the treatment of peptic ulcer.

Design of the Experiment

When there are several separate factors to be assessed they can be tested in a factorial experiment in which the individual factors are combined in all possible ways. In the case of the present study, in which three therapeutic agents—namely, stilboestrol, phenobarbitone, and a gastric diet—were to be tested, the full range of combinations was eight. If S signifies that a patient received stilboestrol, while s signifies that he did not, and if P and p are used in a similar sense for phenobarbitone, and D and d for a gastric diet, the possible combinations are as follows:

SPD SPd SpD sPD Spd sPd spD spd

Provided eight patients are treated with this set of combinations of treatment, it can be seen that the four receiving stilboestrol resemble the four not receiving stilboestrol in respect of the other types of treatment, thus:

Receiving Stilboestrol (*S*): PD, Pd, pD, pd.
Not Receiving Stilbœstrol (*s*): PD, Pd, pD, pd.

Therefore any striking difference between the course of the four patients receiving stilboestrol from that of the four not receiving stilboestrol can reasonably be attributed to the effect of stilboestrol and not to the other treatments.

Likewise it can easily be demonstrated that the four patients receiving phenobarbitone resemble exactly the four patients not receiving phenobarbitone in respect of the other two treatments they receive. The same is true for those on a gastric diet and those not. Hence the therapeutic effects of phenobarbitone and of a gastric diet are readily observed.

Of course eight subjects are too few in most instances to form an experimental group, but, provided some multiple of eight is used as the final number, the general conclusions reached above hold true.

In the present study 80 patients were used, each consecutive group of eight patients being allotted at random to the eight possible combinations of treatment. In statistical terminology this type of layout is known as randomized blocks. This term, like so many others used in modern statistical methods, derives from agricultural research in which a block consists of a number of individual plots of land, whereas in the present study the block represents a group of eight individual patients admitted consecutively to the trial.

From what was said above it can be seen that the effect of the three factors can be assessed with as great precision as if three equally large but separate studies were made, each dealing with one of the three factors. The only exception to this is if two of the factors interact, in which case such a factorial design is the only precise method of measuring the degree of interaction. In relation to therapeutic studies, a positive interaction implies *synergism*, while a negative interaction implies *antagonism* between the therapeutic agents. In the event, no evidence of interaction was found in the present study, which can therefore be regarded simply as being the equivalent of three separate therapeutic trials in one.

More complete and sophisticated accounts of factorial design are given in appropriate books, such as those by Fisher (1951), Finney (1955), and Cochran and Cox (1957). The present explanation is meant solely for those readers unacquainted with modern statistical methods.

Conduct of the Trial

A master sheet was drawn up with the possible combinations of treatment arranged in randomized blocks of eight. From this, two subsidiary sheets were prepared. The first, which showed which combination of stilboestrol and phenobarbitone should be given to any patient according to his serial number in the trial, was held in the dispensary of the Radcliffe Infirmary. "Dummy" tablets of stilboestrol and phenobarbitone were held in the dispensary, and it was therefore only necessary to prescribe treatment in the following form:

No. 26. Mr. A. J. Smith.
℞ Tab. P, 1 b.d.
℞ Tab. S, 1 b.d.

The pharmacist would then enter the name Mr. A. J. Smith in the corresponding row in his master-sheet and would read off in the corresponding line whether the patient was to have real or dummy tablets of phenobarbitone and real or dummy tablets of stilboestrol. Thus the physician was completely "blind" in respect of which patients were allotted to real or dummy

stilboestrol or phenobarbitone, while still retaining a certain liberty of action if patients appeared to be showing undesirable effects of therapy. To be precise, four patients complained during the trial of sleepiness and fatigue, and, as these symptoms were judged as probably due to phenobarbitone, future prescriptions read tab. P. 1 omne nocte, instead of b.d. Similarly, one young man developed appreciable gynaecomastia, and in him the prescription was changed to read tab. S. 1 daily.

It is not easy to conduct a blind trial of a diet without an elaborate organization, and the physician held the limited master-sheet giving details of which subjects were to be prescribed a gastric diet. It is appreciated that not much certainty attaches to the strict adherence of out-patients to a diet, but, conversely, this criticism can be aimed at all physicians who claim good results from dietary treatment not administered under their personal supervision. As much emphasis as possible was put into encouraging those patients allotted to a gastric diet to adhere to the diet, and they were all provided with a booklet, in use in this hospital, containing the exact details. Likewise, as much encouragement as possible to eat an ordinary diet with their family was given to those subjects not allotted to a gastric diet.

The patients were seen and examined monthly during the trial period. At the end of this time they were examined by barium meal, the radiologist being asked to specify whether he could or could not identify an ulcer crater. Thereafter the patients were seen at three-monthly intervals during the follow-up period until five years had elapsed. Some were treated by surgery during this follow-up period; so far as possible it was left to the family doctor to decide that surgery was necessary because of repeated bouts of symptoms, although a few patients were treated surgically because they developed a major complication of the ulcer.

Selection of Patients.—The subjects were all men with a typical history of duodenal ulcer of at least one year's duration. In every case positive *x*-ray findings had already been made. Before being considered suitable for the trial they were examined by a further barium meal and only admitted if the radiologist could identify an actual ulcer crater. It was explained to each subject that an experiment was being made in treatment and a simple explanation was given of the type of study being made. The patient was left to volunteer for inclusion; none of those invited refused. The patient's family doctor was also consulted and his permission obtained.

Length of Trial Period and Dosages Used.—The actual trial period lasted six months. During this period the patients on real treatment received stilboestrol 0.5 mg. b.d. and phenobarbitone 1 gr. (65 mg.) b.d. The lengthy period of six months was chosen for the administration of the treatments to be tested because it was considered that, even if a treatment proved to encourage healing, it might take a fairly long time for permanent healing to occur in an ulcer which had been present for a number of years. In what follows, the results obtained during and at the end of this six months period are called the short-term results.

The subjects were admitted between 1952 and 1954 to the trial. Thereafter their progress was followed for a further five years, and during 1958 and 1959 their final state was assessed on both clinical and radiological grounds.

It is convenient to consider the results on both a short-term and a long-term basis.

Short-term Results

The short-term results refer to the clinical findings during the six-months trial period and to the radiological findings at the end of this time.

Clinical Response to Treatment.—During the six-months trial period 13 of the 80 patients suffered from a bout of typical ulcer symptoms which were bad enough to make them stop working. These symptoms were treated with rest and alkalis in addition to the trial therapy. Table I shows how these exacerbations of symptoms were related to the three types of treatment under test. It will be seen that stilboestrol appeared to have a definite effect in reducing the liability to ulcer symptoms, because all but one of these clinical relapses occurred in patients not receiving stilboestrol. This difference between the patients treated with stilboestrol and those not so treated is highly significant in a statistical sense. On the other hand, neither phenobarbitone nor a gastric diet had any marked influence on the liability to an exacerbation of symptoms.

Radiological Response to Treatment.—At the end of the six-months trial period all the patients were re-examined by barium meal. At this time the radiologist was unable to identify an ulcer crater in 24 patients; among these, some had duodenal caps which had become radiologically normal, while others still showed residual deformity although no crater could be identified (see Figs. 1). When the occurrence of radiological healing of the ulcer is related to the various treatments in use, the findings are those given in Table II. It will be seen that half of the subjects receiving stilboestrol

TABLE I.—*Short-term Clinical Responses. Number of Clinical Relapses Occurring in Relation to Type of Therapy*

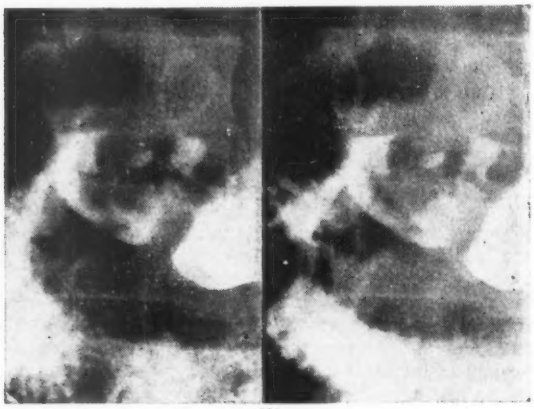
Treatment	No. of Patients	No. Suffering from Clinical Relapse	Significance of Difference
In Relation to Stilboestrol			
Stilboestrol	40	1	Highly significant
Control	40	12	$P<0.01$
In Relation to Phenobarbitone			
Phenobarbitone	40	7	Not significant
No phenobarbitone	40	6	
In Relation to Diet			
Gastric diet	40	7	Not significant
Ordinary ,,	40	6	

TABLE II.—*Short-term Radiological Responses. Number of Patients Showing Radiological Healing of Ulcer in Relation to Type of Therapy*

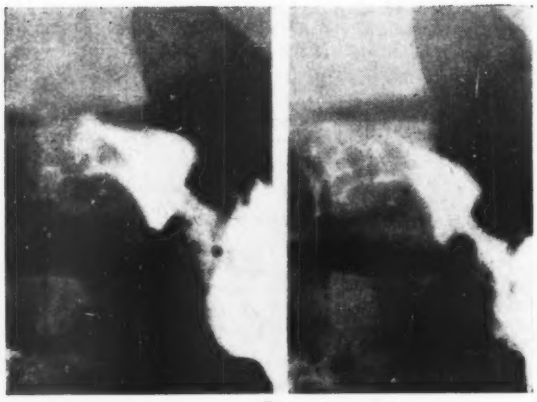
Treatment	No. of Patients	No. Without Crater on Barium Meal at End of Treatment	Significance of Difference
In Relation to Stilboestrol			
Stilboestrol	40	20	Highly significant
No stilboestrol	40	4	$P<0.01$
In Relation to Phenobarbitone			
Phenobarbitone	40	13	Not significant
No phenobarbitone	40	11	
In Relation to Diet			
Gastric diet	40	10	Not significant
Ordinary ,,	40	14	

showed radiological healing of the ulcer compared with only one-tenth of those not receiving this treatment, a difference which statistically is highly significant. On the other hand, neither phenobarbitone nor putting the patient on a gastric diet had any substantial influence on the chance of radiological healing.

Summary of Short-term Results.—In brief, of the three agents tested, only stilboestrol had any beneficial influence on the clinical course and on the radiological evidence of healing. So far as stilboestrol is concerned, freedom from severe symptoms was almost universal during the six-months trial period among the subjects receiving it, but disappearance of the ulcer crater on barium-meal examination occurred in only 50%, though this was five times more frequent than in the other subjects.



(A)



(B)

FIG. 1.—Radiographs showing (A) duodenal ulcer before treatment, (B) normal duodenal cap in the same patient after treatment.

Long-term Results

The long-term results are discussed purely in relation to stilboestrol therapy because there is no indication that phenobarbitone or diet had any major influence on either the short-term or the long-term course of the disease. For stilboestrol it is of importance to know whether the relatively favourable picture presented at the end of the six-months treatment period was preserved or lost during the follow-up stage.

TABLE III.—*Long-term Results in Relation to Treatment With Stilboestrol*

	Stilboestrol Group	Control Group
Prolonged clinical remission with radiological healing	24 (61·5%)	11 (27·5%)
Symptoms persis ing and/or radiological evidence of ulcer crater present	6 (15·4%)	11 (27·5%)
Treated by partial gastrectomy (including 1 patient who died while awaiting operation)	9 (23·1%)	18 (45·0%)
Total	39* (100%)	40 (100%)
Significance of difference between stilboestrol group and control group	Highly significant P<0·01	

* The patient who was lost sight of during the follow-up period has been excluded.

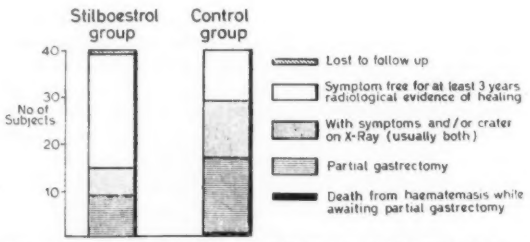


FIG. 2.—Long-term result in relation to stilboestrol therapy during the six-months trial period.

Table III and Fig. 2 show that the relatively favourable picture presented by the stilboestrol-treated patients at the end of the trial period is still present five years later. During the follow-up period there were some patients in both the stilboestrol-treated group and the control group who showed radiological evidence of healing of the ulcer in addition to enjoying a prolonged period of freedom from symptoms. At the other extreme, a number of patients were brought to surgery, sometimes because of a major complication but usually because of recurrent bouts of ulcer symptoms which were judged sufficient to merit definitive surgery. Between these two categories of patient were some who either continued to have bouts of symptoms or to show radiological evidence of an ulcer crater (both these features usually being present) but in whom definitive surgery had not been judged to be necessary by the time the follow-up period ended.

Effect of Stilboestrol in Relation to Length of Ulcer History

Detailed analysis of the data has shown that the only factor which appears to be relevant to the action of stilboestrol is the length of ulcer history before treatment. Table IV and Fig. 3 show the results when the patients in the stilboestrol and control groups are subdivided into those with a long history of duodenal ulcer (more than 10 years) and those with a short history (less than 10 years). It can be seen that in patients with a long history of ulcer this form of treatment had a comparatively small effect, for their prognosis was not sharply dissimilar from that of the control patients; in both treatment groups prolonged freedom from symptoms accompanied by radiological evidence of healing was shown by only a minority. The picture is completely different when only the patients with a shorter

TABLE IV.—*Long-term Results in Relation to Length of History of Duodenal Ulcer Before Entry Into the Therapeutic Trial*

Long-term Results	Ulcer History of Less than 10 Years		Ulcer History of 10 Years or More	
	Stilb. Group	Control Group	Stilb. Group	Control Group
Prolonged clinical remission with radiological healing	19 (79·2%)	8 (33·3%)	5 (33·3%)	3 (18·8%)
Symptoms persisting and/or radiological evidence of ulcer crater present	2 (8·3%)	7 (29·2%)	4 (26·7%)	4 (25·0%)
Treated by partial gastrectomy	3 (12·5%)	9 (37·5%)	6 (40·0%)	9 (56·2%)
Totals	24 (100%)	24 (100%)	15 (100%)	16 (100%)
Significance of difference between stilboestrol group and control group	Highly significant $P<0.01$		Not significant	

history of ulcer are considered. The differences between the stilboestrol group and the control group are then striking. Indeed, for all practical purposes it can be said that the beneficial effect of stilboestrol was confined to the men with a relatively short history of ulcer. In them this form of treatment more than doubled the chance of a "clinical and radiological five-year cure," while partial gastrectomy was judged to be necessary in only one-third as many as in the control patients. Although stilboestrol was far from being universally effective, it emerges as having a definitely beneficial effect upon the long-term course of duodenal ulcer in men, provided the length of ulcer history is not greater than 10 years.

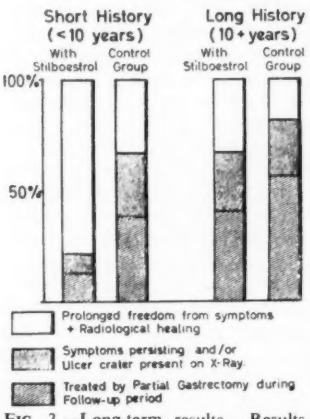


FIG. 3.—Long-term results. Results in relation to (*a*) stilboestrol therapy, and (*b*) length of ulcer history before starting in the trial.

Prognostic Value of the Radiological Findings

An impressive feature of the results was the prognostic significance of the *x*-ray findings at the end of the six-months trial period. During the subsequent five years all but one of the 24 subjects who showed radiological healing at the end of the trial period remained symptomatically normal and were radiologically healed. The one exception had no dyspeptic symptoms but suddenly developed a melaena. In view of the past history of ulcer it was decided to treat him surgically after he had recovered from the bleeding, and partial gastrectomy was carried out; however, no evidence of an existing duodenal ulcer (or gastric ulcer) was found at operation, and it appears possible that the haemorrhage was due to an acute ulcer or erosion, which had healed between the bleed and the operation and which was unrelated to his previous chronic duodenal ulcer. Among the patients who still showed *x*-ray evidence of an ulcer crater at the end of the six-months trial period a number became symptomless and showed radiological evidence of healing during the next five years. However, the great majority suffered from recurrent bouts of symptoms, and a considerable number were brought to surgical operation because these symptoms were severe, including four patients who suffered from the complications of haematemesis or perforation. Of these patients who were treated surgically, a duodenal ulcer was found in every patient except one. In him there was a healed duodenal ulcer and an actual gastric ulcer on the lesser curve of the stomach. A gastric ulcer in this situation is well known among gastroenterologists to occur as a not infrequent sequel to healing of a duodenal ulcer, a course of events which has excited comment from a number of writers, including Daintree Johnson (1955, 1956). In any event, it can be seen that the fact that a patient was brought to surgical operation can be used in this study as an almost completely accurate piece of evidence that an ulcer was still present. When the long-term results are reclassified to show their relationship to the radiological findings at the end of the trial period, it becomes evident that these radiological findings furnish an excellent general guide to the future course of the ulcer (Table V).

TABLE V.—*Relationship of Long-term Results to Short-term Radiological Response*

Long-term Results	Short-term Radiological Response	
	Ulcer Crater Absent	Ulcer Crater Still Present
Prolonged clinical remission with radiological healing	23 (95·8%)	12 (21·8%)
Symptoms persisting and or radiological evidence of crater	0 (0·0%)	17 (30·9%)
Partial gastrectomy	1* (4·2%)	26 (47·3%)
	24 (100%)	55 (100%)

* As described in the text, no evidence of an existing ulcer was found in this patient, who was operated upon because of melaena.

Complications of Treatment

Before this study was begun an eminent authority on stilboestrol gave it as his opinion that side-effects would be negligible with the particular dose used. In the event, it was found that diminution or loss of sexual potency was usual and that gynaecomastia also occurred. The gynaecomastia was minor and did not set in until about the fourth or fifth month of treatment, being then evident as a firm swelling of the breast tissue about half an inch (1.3 cm.) in diameter which was palpable but usually not large enough to cause visible swelling of the breast; this change promptly reversed itself when treatment was stopped at the end of the trial period. Full sexual potency also returned in a week or two after stopping treatment, a finding which agrees with endocrinological opinion that the effects of oestrogens on the testes are completely reversed when administration ceases (Bishop, 1958).

Death During the Follow-up Period

One patient died from a massive haematemesis which occurred on the evening before partial gastrectomy was due to be performed. The details are of some interest and are therefore briefly recorded.

The patient was aged 60 when first seen. He was among those not receiving stilboestrol. At the end of the trial period a duodenal ulcer was still present on the *x*-ray film. During the five-year follow-up he continued to have episodes of ulcer pain, but these were not severe and were treated with alkalis and rest along traditional lines. At the end of the five-year follow-up, the barium-meal examination showed the duodenal ulcer to be still present, and in addition the radiologist observed a soft rounded shadow in the chest in the right infraclavicular region. He judged

the appearances to be strongly in favour of this being a tuberculous lesion (Assmann's focus) and was confirmed in this view by finding a smaller shadow in the same position on an earlier chest film taken during a barium-meal examination in the middle of the follow-up period. The patient was admitted to a sanatorium in Oxford, when confusion arose because malignant cells were identified in the sputum by Dr. A. I. Spriggs, while no tubercle bacilli were found. At this time he developed ulcer-symptoms of greater severity than ever before and it was therefore decided, after consultation between the chest physician and myself, that, in spite of the findings relevant to the chest, he should be transferred to the Radcliffe Infirmary for partial gastrectomy. As already mentioned, a sudden massive haematemesis on the evening before operation proved fatal. A post-mortem examination showed (1) a duodenal ulcer which had eroded into the pancreatico-duodenal artery, (2) a tuberculous lesion corresponding to the soft intraclavicular shadow on the chest *x*-ray film, and (3) a tiny carcinoma of the bronchus.

Coronary Thrombosis

Since this study began, much interest has been shown in the fact that oestrogens will depress the cholesterol and β-lipoprotein levels of the blood, and consequently may have some protective action against atheroma and coronary thrombosis. For what it is worth, it may be mentioned that coronary thrombosis occurred in only one of the patients during the follow-up period, and it did so in a patient who had not been treated with stilboestrol.

Discussion

Three main aspects of the present study merit discussion.

1. Importance of the Radiological Findings

The only satisfactory radiological evidence of the presence of a duodenal ulcer is the identification of an unequivocal ulcer crater. In the early days of diagnostic radiology the identification of the actual crater was thought to be exceptional, but to-day, with modern apparatus and techniques, a skilled radiologist who is willing to take care over the examination can demonstrate the crater in a large majority of patients. There are a number of secondary signs of duodenal ulcer, such as deformity of the duodenal cap, a small cap (phthisis bulbae), irritability of the cap, and the presence of pseudodiverticula, which may constitute presumptive evidence of duodenal ulcer strong enough for the every-day practice of clinical medicine. For research purposes these secondary signs are inadequate, and it is imperative to confine tests of new remedies to those subjects in whom the cardinal radiological sign of demonstration of the actual ulcer crater can be obtained. When this is done, it appears from the present study that the radiological findings at the end of treatment are of prime importance because they are closely correlated with the future clinical course.

In duodenal ulcer we are especially interested in what happens over the course of a number of years, but studies employing the stringent test of prolonged clinical follow-up, as the present one has done, suffer from the major disadvantage of being extremely time-consuming. Anything which can render unnecessary this tedious method of obtaining valid information is to be welcomed. It appears that intelligent use of the radiological findings will permit such a quickening of tempo in the testing of new remedies in duodenal ulcer.

With a single exception, all the patients who no longer showed radiological evidence of an actual ulcer crater at the end of the trial period remained symptom-free, with persistent radiological evidence of healing during the next five years; by contrast, most of the remainder had recurrent bouts of symptoms, and only a minority had had a prolonged period when they were free from symptoms and showed radiological healing at the end of the five-year follow-up. It thus appears that when a patient with duodenal ulcer has recurrent bouts of symptoms with complete freedom in between, as a general rule the same ulcer is present throughout. This finding brings out the necessity to develop methods of treatment which cause the ulcer to heal rather than to rely on methods which simply alleviate the immediate symptoms.

2. Stilboestrol and Other Oestrogens as a Practical Therapy

Stilboestrol cannot be regarded as an ideal treatment for duodenal ulcer in men, because it is not universally beneficial and it produces side-effects. It should certainly not be used in patients with a long history of duodenal ulcer (more than 10 years), for there is no evidence of any major improvement in the prognosis of such long-standing cases. In those with a short history it is a question of deciding whether the benefits outweigh the disadvantages; or, alternatively, whether the benefits can be retained while the disadvantages are minimized. One possibility is that a course of treatment much shorter than the one employed in the present study would still retain the benefits. This possibility will demand a properly controlled trial for its elucidation, but the results obtained in a few patients given a three-months course of treatment during the follow-up period have appeared sufficiently favourable at any rate to justify such a trial.

The other main possibility is to use an oestrogenic agent other than stilboestrol. The naturally occurring oestrogens are unlikely to have any advantages over stilboestrol because their biological properties appear to be virtually identical with those of this agent (Dodds, 1955), so that there is no reason to suppose that they would have more favourable healing properties in relation to the same measure of feminizing power. A more encouraging possibility is the use of steroidal analogues that retain many of the properties of the naturally occurring oestrogens while having only slight feminizing effects. Such analogues have so far been developed and tested in relation to two main properties of the oestrogens outside their feminizing activity. On the one hand, the oestrogens are anabolic agents that have proved useful in diseases such as osteoporosis (Henneman and Wallach, 1957), and it has been shown that these anabolic properties can be retained when the molecule is altered so that feminization is diminished. On the other hand, the present search for measures which may be preventive against coronary thrombosis has shown that oestrogenic analogues with little feminizing power can still have as much effect upon the lipoprotein fractions of the blood as natural oestrogens (Rivin, 1959).

It goes without saying that the only test of whether these or other "non-feminizing" analogues of the oestrogens are useful in duodenal ulcer will be the hard facts obtained in properly executed and controlled therapeutic trials.

3. Theoretical Considerations of the Mode of Action of Oestrogens in Duodenal Ulcer

If we take the present study as providing sufficient evidence that an oestrogenic agent increases the chance

of obtaining healing of a duodenal ulcer in a man, it is fascinating to speculate on its possible mode of action, especially as such speculation may point the way to future studies.

An obvious possibility is that oestrogens diminish the secretory activity of the stomach. It was mentioned in the introduction that Winkelstein (1936) found no constant change in the gastric secretion of dogs when treated with an oestrogen which appeared to cause ulceration around an artificial gastric stoma to heal. On the other hand, Ojha and Wood (1950) found that administration of stilboestrol to cats caused a diminution in gastric secretion which appeared to be progressive during the course of their experiments. Similar studies do not seem to have been made in man, although Clark and Tankel (1954) have reported that in pregnancy (in which circulating oestrogen levels are high) the acid secretion of the stomach shows no fall. Systematic studies of gastric secretion were not made in the therapeutic trial now reported.

Another possibility is that oestrogens have a beneficial effect upon healing that is largely irrespective of the type of lesion. For many years there have been reports that oestrogenic preparations applied locally accelerate the healing of chronic ulcer of the skin; references to this work are given in an extensive review of wound-healing by Arey (1936). This early work is not convincing because adequate controls were not used. Such a criticism cannot be levelled at the work of Sjövall (1953, 1954), who has demonstrated beyond all reasonable doubt that the administration of oestrogens improves the rate of healing of vaginal wounds in rats, while testosterone has no beneficial effect. Sjöstedt (1953) has likewise shown in controlled clinical studies that oestrogens accelerate the healing of perineal and vaginal operation wounds in post-menopausal women, so that they heal as rapidly as similar wounds in young women.

A number of observations suggest that oestrogens exert widespread effects in the body quite outside those we label as feminizing effects. Bullough (1946, 1955) considers that oestrogens are general stimulators of mitosis, which might account for any healing properties they can be shown to possess. The metabolic actions of the oestrogens in increasing protein anabolism and depressing blood cholesterol and lipoprotein levels have been mentioned earlier in the discussion; certainly the anabolic actions might be highly relevant to healing.

Even more relevant may be the results of modern biochemical research into the actions of oestrogens at tissue level. It is known that oestrogens are widely distributed throughout the whole plant and animal kingdoms, and this fact has stimulated inquiry into their metabolic functions outside those feminizing powers which in medicine have appeared to be almost their sole characteristic of note. It has been shown that a particular part of the steroid molecule must be present for a substance to act as an oestrogen. Finally, it has been shown that steroids with this particular configuration (which includes all the naturally occurring human oestrogens and those synthetic agents like stilboestrol which mimic their biological actions) act as coenzymes and facilitate hydrogen exchange in nuclear reactions in a variety of tissues (Hurlock and Talalay, 1958). In the particular context of the present study, this finding reinforces what was earlier said about the possibilities of finding analogues of stilboestrol with healing powers but minimal feminizing activity.

H. M. Sinclair (1959, personal communication) has suggested that the results of the present study can be interpreted in the light of duodenal ulcer being one of the manifestations of lack of essential fatty acids (E.F.A.), in which he believes our modern diets to be seriously deficient (Sinclair, 1956, 1958a). He remarks: "This deficiency causes a structural defect in cell membranes and connective tissue, and the body in consequence becomes increasingly susceptible to injurious agents. Among these are infections, ultra-violet light, *x*-rays, chemical carcinogens, and hydrochloric acid in the duodenum. It is possible, therefore, that a relative deficiency of E.F.A. could play a part in the aetiology of . . . duodenal ulcers. . . . The requirement of E.F.A. in lower animals is about seven times greater in males than in females during the reproductive period" (Sinclair, 1958b). Of course, the most direct way of putting Sinclair's hypothesis to the test in duodenal ulcer would be to try the effect of feeding supplements of essential fatty acids to men with duodenal ulcer under the controlled conditions of a formal therapeutic trial; such a study is already planned.

Summary

The results are presented of a therapeutic trial in chronic duodenal ulcer in men. Three agents were tested—namely, stilboestrol, phenobarbitone, and a gastric diet. The trial was a controlled one, and was also "double blind" so far as phenobarbitone and stilboestrol were concerned.

The trial was conducted as a factorial experiment in which all eight possible combinations of the three agents were used within the framework of a randomized block design.

Eighty patients were admitted to the trial between 1952 and 1954. The actual trial period lasted six months, and the subjects were then kept under observation for another five years.

Neither phenobarbitone nor putting the patients on a gastric diet had any material influence on either the short-term or the long-term course of the disease.

Stilboestrol had a beneficial effect on both the short-term and the long-term course of the disease.

The beneficial effect of stilboestrol was chiefly evident in those subjects with an ulcer history of less than 10 years. In such subjects treated with stilboestrol, prolonged "clinical and radiological cure" was more than twice as common as in the controls, while surgical treatment was judged to be necessary in only one-third as many.

The radiological findings at the end of the trial period were found to furnish an excellent general guide to the future clinical and radiological course of the disease.

The implications of these findings are briefly discussed. The possible use of stilboestrol as a practical form of therapy will probably depend on whether equally good results can be obtained with a shorter course of treatment to minimize side-effects of therapy. However, there is the more promising possibility that steroidal analogues with minimal feminizing powers but equally beneficial healing properties can be found.

For the present, this whole approach to the treatment of chronic duodenal ulcer should be regarded as experimental.

I am deeply indebted to Dr. Kenneth Lumsden for his painstaking work on the radiological aspects of this study. Before beginning the study I enjoyed the advantage of discussing possible experimental designs with Dr. D. J. Finney,

F.R.S., now reader in statistics, Aberdeen University, but at that time lecturer in the design and analysis of scientific experiment, Oxford University, and it is a pleasure to record my thanks to him. I am grateful to several surgical colleagues who referred patients to me, and especially to Professor G. J. Fraenkel.

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NON-CLOSTRIDIAL GAS INFECTIONS IN DIABETES MELLITUS

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The abnormal susceptibility of diabetics to infection is well known. It may result in a rapidly spreading pyogenic infection starting from a trivial local lesion, sometimes caused by organisms which usually are non-invasive and comparatively non-virulent. Occasionally such an infection may be accompanied by marked production of gas in the tissues, and the condition may simulate clostridial gas-gangrene.

The occurrence of "gas infections" in diabetes was first recorded by Chiari in 1893; he described the formation of gas due to the colon bacillus in the gangrenous tissues of the leg of a diabetic. He believed that the diabetic state favoured the production of gas in the soft tissues. Hitschmann and Linderthal (1899) reported a further case of a diabetic clinically thought to have gas-gangrene, but on culture *Escherichia coli, Streptococcus pyogenes*, and an unidentifiable rod were the only organisms obtained; only the coliform bacillus produced gas when grown in culture media. Warren (1938) described the cases of two diabetics with a clinical diagnosis of gas-gangrene from whom the only organisms obtained on repeated aerobic and anaerobic culture were *E. coli* and staphylococci. Gillies (1941) described four diabetics with infections due to the colon bacillus, alone or in association with other organisms. One of these cases had an infection of the urinary tract with perirenal gas; the other three had gas in the subcutaneous tissues of the lower extremity.

Spring and Kahn (1951) reported one case of their own, and two further cases from the records of the Bronx Hospital from 1932 to 1950, of non-clostridial gas infections in diabetics. The organisms obtained on culture in two of these cases was *E. coli*, but in the third case smear showed Gram-positive cocci, Gram-negative bacilli, and Gram-positive bacilli, with no growth on culture. Altemeier and Culbertson (1948) listed five cases of "non-clostridial crepitant cellulitis" from the literature and recorded 12 further cases, at least two of which were diabetics. The organisms most commonly present included: *aerobic*—non-haemolytic streptococci and *E. coli*; and *anaerobic*—*Bacterium melaninogenicum* and anaerobic streptococci.

This paper describes the cases of four elderly patients who developed rapidly spreading non-clostridial "gas infections" of the leg. All four were diabetics of long standing with peripheral neuropathy and vascular disease. The infections in Cases 1 and 2 were at first thought to be examples of clostridial gas-gangrene.

These cases are of interest for three reasons. First, owing to the absence of much pain the diagnosis was not suspected until the infection was far advanced. Second, in one of the cases deterioration continued despite treatment with antibiotics to which the organisms were subsequently shown to be sensitive. Finally, early diagnosis from clostridial gas-infection was difficult and led to uncertainty regarding the best method of treatment.

Case 1

A retired typist aged 60, whose diabetes had been discovered in 1952, had been controlled on soluble insulin by her own doctor. She had previously been admitted to another hospital in November, 1958, with multiple abscesses of both thighs, one of which required surgical drainage. Culture of swabs from these abscesses yielded a coagulase-positive *Staphylococcus aureus*, which was reported as resistant to several antibiotics. Treatment with a course of tetracycline was carried out with good response, and eventually she was discharged home, having been re-established on insulin zinc suspension. She was noted at this time to have evidence of neuropathy and vascular disease.

On February 22, 1959, she was admitted as an emergency case with a deep discharging abscess of the right buttock that had been present for some weeks. There was associated oedema of the upper right thigh, which was 2½ in. (6.3 cm.) greater in circumference than the left. There was no tenderness of the thigh. A type 80 *Staph. aureus*, resistant to penicillin, streptomycin, and tetracycline, was cultured from the abscess, and treatment with chloramphenicol and erythromycin 0.5 g. statim then 0.25 g. eight-hourly of each, was begun.

Her condition deteriorated and on February 26 she complained of pain in the right leg. Examination revealed evidence of gas in the subcutaneous tissues with marked crepitation extending down the leg to the posterior aspect of the right ankle. Clostridial infection was diagnosed. In view of this she was given 5 mega units of crystalline penicillin and taken to the theatre. At operation multiple incisions confirmed the presence of large quantities of watery pus and gas, mainly in the subcutaneous tissues but also beneath the deep fascia and in between the muscle bundles.

The muscles appeared viable and contracted, and bled on biopsy. Aerobic and anaerobic cultures of three separate specimens of pus and two specimens of muscle revealed only *Str. faecalis* and bacteroides. The latter, which was present in very large numbers, was later identified as *Bacteroides varius* (Bergey, 1948). Both organisms were sensitive to chloramphenicol and erythromycin and resistant to penicillin and streptomycin. Section of muscle from the thigh showed healthy fibres with large numbers of Gram-negative bacilli and a few Gram-positive cocci lying between the bundles.

The patient's condition continued to deteriorate, and on March 5 cultures of pus from the wounds yielded klebsiellae, *Bacteroides varius*, and yeasts. On March 10, in view of spreading gangrene of the leg, a high above-knee amputation was carried out. The stump became grossly infected with *Bacteroides varius, Pseudomonas pyocyanea*, klebsiellae, and a few colonies of a clostridium. Because of the presence of the last-mentioned organism, 40,000 units of anti-gas-gangrene serum was given intravenously and crystalline penicillin 2 mega units six-hourly was started—both unnecessary measures because the clostridium was later proved to be *Clostridium sporogenes*, a non-pathogen. The patient died on March 19. Post-mortem examination revealed evidence of septicaemia and acute bacterial endocarditis caused by *Ps. pyocyanea*.

Case 2

A housewife aged 60 had been a known diabetic for 16 years. For the past four years she had been noted as showing evidence of peripheral neuropathy, retinopathy, and a chronic septic lesion on the left fifth toe for which surgery had been advised and refused.

On admission to hospital on March 9, 1959, there was a foul-smelling, necrotic, discharging area on the sole of the right foot, with a smaller lesion on the left foot. She showed clinical evidence of widespread vascular disease and some renal damage as reflected by a blood non-protein nitrogen of 50 mg./100 ml. She was stabilized on insulin with reasonably good control of her diabetes as judged by urine sugar analysis. The foot lesions were treated with bed rest and local toilet.

Swabs taken on admission from the ulcers of both feet yielded *E. coli* and a non-haemolytic aerobic streptococcus which was sensitive to penicillin. She was given an eight-day course of crystalline penicillin, 500,000 units b.d. intramuscularly.

Her condition deteriorated. Her legs and feet were examined daily, and on March 25 the right calf was found to be swollen, with well-marked crepitation spreading up the right calf from the gangrenous patch on the foot. A diagnosis of "gas-gangrene" was made. She was given 1 mega unit of crystalline penicillin and taken to the theatre that afternoon, where an above-knee amputation was carried out. However, she collapsed and died at the end of the operation.

At the time of operation material for culture was obtained from the ulcerated area on the foot and by direct swab and muscle biopsy through a clean incision made in the calf some 12–13 in. (30.5 to 33 cm.) from the original lesion. From all these materials the only organisms obtained on culture were micrococci and *E. coli*. The latter were present in very large numbers in the calf.

Post-mortem examination showed the cause of death to be *E. coli* septicaemia and septic infarction of the spleen with perisplenic abscess.

Case 3

A railway portress aged 50, a known diabetic for nine years, was poorly controlled on insulin. She was admitted to hospital on May 11, 1959, in coma as an emergency case. Two years previously she had been found to have evidence of diabetic retinopathy, peripheral neuropathy, and vascular disease. Three months before this admission she had developed a right hemiplegia after a cerebrovascular accident.

On admission she was stuporous, with a raised respiratory rate, a temperature of 99.5° F. (37.6° C.), and signs of pneumonia and pleurisy. There was an ulcer on the posterior aspect of the right ankle. The diabetes was fairly well controlled with a six-hourly regime of insulin and glucose, and the infection was treated with intramuscular injection of crystalline penicillin 1 mega unit, followed by 0.5 mega unit six-hourly. Despite this she continued to run a temperature of 101–102° F. (38.3–38.9° C.), her condition deteriorated, and she died four days after admission. At necropsy one and a quarter hours after death an abscess was found which extended from the ankle to the middle of the right thigh. It contained foul-smelling watery pus and gas. Crepitus was detected in the thigh, but it is not certain that this was present before death.

Aerobic and anaerobic cultures of specimens of pus obtained from the subcutaneous tissues at three different sites in the leg and thigh, and of biopsies of muscle from the thigh and of the original ulcer, yielded a profuse growth of *E. coli* with a moderate growth of an anaerobic streptococcus sensitive to penicillin.

Additional findings at necropsy were old myocardial and cerebral infarction with recent bronchopneumonia.

Case 4

A retired European-Indian railway worker aged 63 had been a diabetic for 16 years. He had not taken insulin, despite advice, until his attendance at a clinic in this hospital a year prior to death. On examination at this time he was noted to have neuropathy, vascular disease, retinopathy, and albuminuria; there was a small ulcer on his right toe and his electrocardiogram showed a right bundle-branch block. During his follow-up attendances the ulcer gradually increased in size and a further lesion developed on his left heel despite good control of his diabetes on insulin as judged by urine sugar analysis. In view of these ulcers he was admitted to hospital for conservative treatment on May 20, 1959, but there was little improvement, and he was discharged home on August 1.

On September 1 he was readmitted as an emergency case. He was drowsy, with uncontrolled diabetes, a raised blood non-protein nitrogen, and some congestive cardiac failure. The diabetes was brought under control with insulin and his condition slightly improved.

Routine examination of the leg on September 10 showed crepitation in the left calf, spreading upwards from the lesion on the left heel. Lateral *x*-ray films demonstrated gas in the soft tissues around the heel and in the lower part of the leg. A swab taken from the heel lesion at the time grew a heavy growth of *E. coli* sensitive to streptomycin, chloramphenicol, and tetracycline. He was started on crystalline penicillin, 1 mega unit b.d., and chloramphenicol, 250 mg. six-hourly, and taken to the theatre, where mid-thigh amputation was carried out. Culture of calf muscle, taken some 8 in. (20 cm.) from the heel lesion, produced a good growth of *E. coli*. After amputation his condition somewhat improved for the next 10 days. However, it then deteriorated again, and he developed severe ischaemic pain in the legs, thrombosis of the radial artery, and a heavy proteus urinary infection. He developed a terminal bronchopneumonia and died on October 3.

Discussion

The true incidence of non-clostridial "gas infection" is difficult to assess. Small quantities of gas are not infrequently found in intra-abdominal abscesses caused by intestinal organisms such as coliform bacilli, streptococci, and bacteroides. The occurrence of a virulent rapidly spreading infection in a limb, accompanied by the production of large quantities of gas due to non-

clostridial infection, would appear to be most unusual, and, except in diabetes mellitus, is outside our experience.

The combination of vascular disease and neuropathy with severe diabetes evidently can so lower the patient's resistance to infection that organisms which normally possess little virulence can very rapidly invade the limb, starting from a small local lesion such as an ulcer on the foot. It is possible that the increased glucose in the tissue may enhance the gas-production by organisms such as *E. coli*. The rapid multiplication of the bacteria may result in the production of gas in sufficient quantity to be clinically apparent. The ability of this bacillus to produce gas in culture media containing carbohydrate is well known, and a parallel exists in the pneumaturia of diabetes, which has been reviewed by Foord *et al.* (1956), who have suggested a similar mechanism. The accumulation of gas in the affected limb may also be enhanced by the impairment of circulation delaying absorption.

Spreading infection in the limb of a diabetic, whether gas be present or not, requires prompt treatment, and early recognition of the condition is essential. The diabetic neuropathy and possibly the toxaemia appear to minimize the pain usually experienced in acute infections of the limb and also the awareness of other new symptoms; the limb must be repeatedly and carefully examined.

In Case 1, oedema of the thigh without tenderness was the first sign of spread. The spread of crepitus in infection commonly leads to the diagnosis of a clostridial infection. The clinical picture in these cases, however, is more in keeping with that described by MacLennan (1943) of the similar anaerobic streptococcal cellulitis and myositis seen in the Middle East Campaign. The tempo of the infection is slower than that of clostridial infection. Pain is not so marked, toxaemia is slower in onset, and the temperature and pulse are not as elevated. The diagnosis is confirmed at operation. The gas appears maximal in the fascial layers, and the muscle on biopsy is contractile, and, apart from some oedema, is normal in colour. Immediate search for organisms in pus and muscle should be made. Treatment with antibiotics was disappointing in the one case (Case 1) where the organisms were shown to be sensitive by *in vitro* methods to the antibiotics used. Choice of antibiotics may be complicated by uncertainty of the causative organism, as various bacteria may be cultured from the local lesion. In view of this it may be justifiable to give large doses of more than one antibiotic. Early diagnosis and surgery would appear to be essential for success. In Case 4 it was felt that some measure of success had been achieved, as the ultimate cause of death was unrelated to the initial infection.

Summary

Four fatal cases of non-clostridial gas-infections in diabetics are described and the literature is briefly reviewed.

The organisms cultured from these cases were: Case 1, *Str. faecalis* and *Bacteroides varius*; Case 2, micrococci and *E. coli*; Case 3, *E. coli* and anaerobic streptococci; Case 4, *E. coli*.

The effect of diabetes on the production of large quantities of gas and the enhanced invasiveness of organisms which usually are not markedly gas-forming or invasive is discussed.

The insidious onset of pain is noted and the differential diagnosis from clostridial gas-gangrene is discussed. Emphasis is put on the slower tempo and the findings at operation.

Successful treatment is based on early diagnosis.

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ARGENTAFFINOMA OF THE LUNG WITH CARCINOID SYNDROME

BY

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Malignant carcinoid of the small intestine producing a peculiar complex of symptoms known as the carcinoid syndrome is now well recognized, but a similar condition arising in the lung is rare enough to warrant this report, since only six similar cases have so far been published.

The first description of carcinoid tumours was by Lubarsch (1888), followed by Oberndorfer (1907). In 1914 attention was drawn to the possibility that the chromaffin cells of these tumours could constitute an endocrine reservoir, and Cassidy (1930) reported the case of a young man with an abdominal tumour and hepatic metastases, with flushing of the face and a systolic murmur due to pulmonary stenosis. However, twenty years elapsed before a relationship was established between carcinoid tumours and a certain endocrine symptom-complex. In 1952 enteramine, or serotonin, the specific hormone of enterochromaffin cells, had been identified as 5-hydroxytryptamine, and in the next year serotonin was found in carcinoid tumours. In 1955 the degradation product of serotonin, 5-hydroxy-indole acetic acid, was found in the urine of patients with carcinoid tumours, since when the syndrome of the functioning carcinoid has become widely recognized.

The primary lesion is usually in the gastro-intestinal tract, in which event there are invariably hepatic metastases in those cases presenting the carcinoid syndrome. In a series of 50 cases of ileal carcinoid reviewed by Thorson (1958), 10 had an associated carcinoid syndrome and all of these had hepatic metastases.

On the other hand, of 52 cases of carcinoid of the appendix not one had hepatic metastases or evidence of the functioning syndrome.

There have been several reports of the carcinoid syndrome occurring in association with bronchial adenoma. Kincaid-Smith and Brossy (1956) reported a case in which the carcinoid syndrome developed six years after lobectomy for a bronchial adenoma, the symptoms being produced by hepatic metastases. Stanford *et al.* (1958) report a case of bronchial adenoma with a solitary metastasis and associated carcinoid syndrome. Warner and Southren (1958) reported two cases and mentioned two others in the files of the American Armed Forces Institute of Pathology. Schneckloth *et al.* (1959) reported a further case and Freidman presented another to a meeting of the Australasian College of Physicians in Sydney in 1958.

Case Report

The patient was 62 years old in 1952, when she was referred by a suburban hospital with a three-months history of cough and sputum, one small haemoptysis, and the loss of approximately 3 st. (19 kg.) in weight. Apart from diminished expansion of the left hemithorax, no significant clinical signs were noted, but a chest *x*-ray film (Fig. 1) was suggestive of a tumour involving the upper lobe of the left lung, with elevation of the left dome of the diaphragm, which was paretic. Bronchoscopy was performed without any definite disease being seen, and as the patient rejected the suggestion of thoracotomy, and in fact would not agree to any further investigation, she was merely followed in the out-patient clinic, with progressive *x*-ray films of the chest. These showed no change, and the patient's clinical state did not alter until November, 1958, when she complained of pain in the left upper chest and increasing dyspnoea and when *x*-ray examination showed enlargement of the left-upper-lobe opacity with further shift of the mediastinum to the right.

She declined a recommendation of immediate admission, but agreed to enter hospital in the new year, by which time she had become very dyspnoeic and complained of attacks

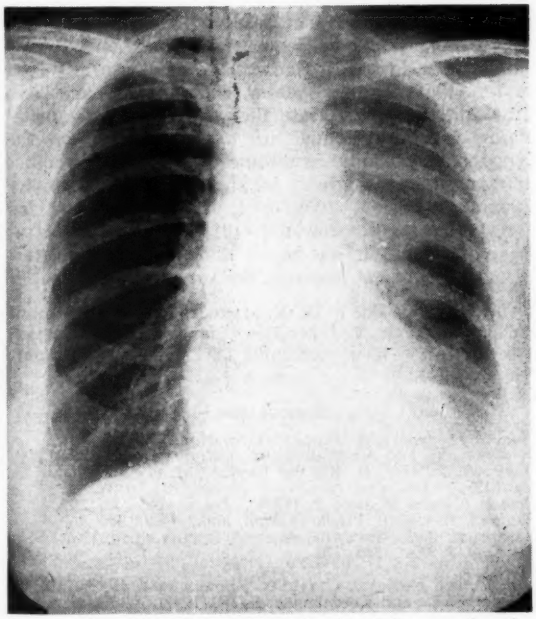

FIG. 1.—*X*-ray film taken on November 11, 1952, suggestive of a tumour involving the upper lobe of the left lung.

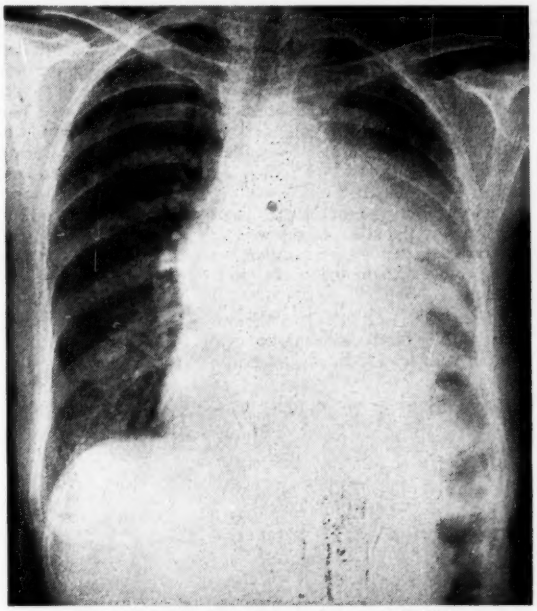

FIG. 2.—*X*-ray film taken on January 19, 1959.

of diarrhoea lasting two or three days, intermittent flushing of the face and upper thorax, and episodes of wheezing. She also had oedema of the legs and a raised jugular venous pressure (4 cm.), these signs subsiding after treatment with digoxin and diuretics. Her chest *x*-ray film was as reproduced in Fig. 2, and subsequently a bronchogram was performed which showed obstruction of the left upper lobe bronchus. At her own insistence she was discharged from hospital at the end of January, but was readmitted in March with recurrence of signs of congestive cardiac failure, there being oedema of both legs, an elevated jugular venous pressure, and hepatomegaly; in addition, there was marked oedema of both hands and forearms, the left more so than the right, and although this fluctuated somewhat it showed no real response to diuretic therapy. Her facies and upper thorax had a dusky cyanotic tint with a number of telangiectases and obvious ecchymoses over both forearms.

At this stage the diagnosis of a functioning carcinoid was suggested and specimens of urine were examined for excretion of 5-hydroxy-indole acetic acid. Daily excretions of 28 to 40 mg. of 5-H.I.A.A. were obtained. After two weeks her hepatomegaly had subsided so that the liver was only just palpable, and a liver biopsy revealed only normal tissue. A basal systolic murmur had been noted on a number of occasions, and an electrocardiogram showed pulmonary P waves but was otherwise normal. She was treated with nicotinic acid 10 mg. b.d., chlorpromazine hydrochloride 25 mg. t.d.s., digoxin 0.25 mg. b.d., and injections of mersalyl twice weekly. Although there was no appreciable change in her oedema, her facial flushing and diarrhoea were greatly relieved. At the request of her relatives she was transferred to a nursing-home, where she died on May 11, 1959.

Post-mortem Findings

The significant portions of Dr. V. J. McGovern's report are as follows.

"*Lungs:* The right lung is very congested and oedematous. The upper lobe of the left lung is entirely replaced by tumour, and this tumour directly invades the regional lymph nodes and has involved the hilar lymph nodes of the right lung. A tongue of tumour projects into the left main bronchus through the main upper-lobe bronchus. On section the tumour is found to have a semi-translucent, white

appearance in some places and a haemorrhagic appearance in others. The heart is normal in all its chambers and valves. There is no lesion present which can be attributed to serotonin. Tumour of the lung is compressing the left pulmonary artery and the pulmonary veins on the left side. *Liver:* The liver appeared normal. *Alimentary Tract:* The appendix had been removed some time in the past, and in the caecum near by there is a secondary carcinoma measuring 1.5 cm. in diameter. There is a further small secondary deposit in the pelvic colon. *Pancreas:* There are several carcinomatous nodules in the head of the pancreas and a small one in the tail. *Adrenals:* Each adrenal gland contains a secondary deposit of tumour, with that on the left side being bigger than the right and measuring 2.5 cm. in diameter.

"*Histology.—Lung:* The tumour is composed of small cells with slightly acidophilic cytoplasm (Fig. 3). The tumour cells tend to be arranged in an alveolar fashion. The

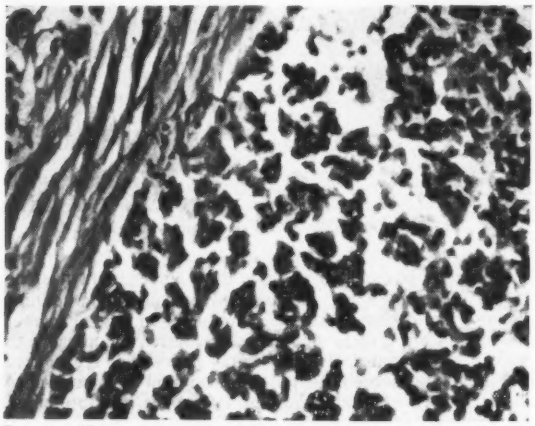

FIG. 3.—Photomicrograph of lung tumour, showing small cells with slightly acidophilic cytoplasm.

tumour in the pancreas and elsewhere has a similar appearance. The tumour does not have any argyrophyl reaction, but this may be due to post-mortem change, the necropsy have been performed 24 hours after death."

Discussion

The diagnosis of carcinoid syndrome depends upon the presence of suggestive symptoms and signs, upon biochemical evidence of excessive production of 5-hydroxytryptamine, and upon histological examination of the primary and metastatic tumours.

Of the clinical features, cyanotic flushes and abdominal symptoms are probably the most common. Although often intermittent, the flushing may be constant and accompanied by telangiectasia or purpura. Diarrhoea and abdominal cramps, with at times the picture of intestinal obstruction, are common. Oedema occurs in the face and arms as well as in dependent parts, and wheezing and dyspnoea are frequent features. Valvular disease of the right side of the heart usually appears late in the course of the illness, with signs of pulmonary stenosis, tricuspid stenosis, or incompetence. In a small number pellagra-like symptoms develop, due to competition by the tumour for dietary tryptophan. In addition there are the clinical signs of the tumour masses, which in most cases include hepatomegaly.

Since the symptoms associated with functioning carcinoid are due to the production of serotonin, which is derived from 5-hydroxytryptophan and ultimately from dietary tryptophan, the finding of an excess of this substance in the blood, or the degradation product 5-H.I.A.A., is clear diagnostic evidence. 5-H.I.A.A. is produced by the action of monoamine oxidase on 5-hydroxytryptamine, and this enzyme is present particularly in the liver and lungs. As a screening test, qualitative estimation of 5-H.I.A.A. can be easily carried out by the Sjoerdsma test. If this is positive then the 24-hour excretion of 5-H.I.A.A. can be estimated; this normally should be between 2 and 9 mg. per 24 hours, but in carcinoid syndrome is mostly between 40 and 2,000 mg.

Histologically, carcinoids are composed of small cells of central nuclei arranged in columns, rosettes, or alveoli. In intestinal carcinoids, granules staining with silver stain can often be demonstrated as in the parent argentaffin cells. The ease of demonstration of these granules diminishes greatly with the time between obtaining and staining specimens, and in the reported cases of functioning bronchial carcinoids no argentaffinity has been demonstrated. Jackson and Konzelmann (1937) consider that bronchial carcinoids are probably derived from neural elements in the bronchus.

In the case here reported most of the features of the carcinoid syndrome were present without hepatic metastases. Since the tumour was in the lung one can assume that 5-hydroxytryptamine was liberated direct into the pulmonary veins and so to the general circulation, where it would exert its endocrine effects before being inactivated by passage through the lungs or liver. This could account for the fact that the symptoms were quite marked despite a level of 5-H.I.A.A. excretion lower than in most reported cases.

The two bronchial carcinoids reported by Warner and Southren (1958) had hepatic metastases. As both these patients had previously had resection of the primary bronchial lesion, either hepatic or extraportal metastases were obviously essential for the production of the carcinoid syndrome. The cases of Kincaid-Smith and Brossy (1956) and of Schneckloth *et al.* (1959) were similar in this regard. Conversely, the case of Stanford *et al.* (1958) had a solitary extrahepatic metastasis. This and the present case indicate that hepatic metastases are not essential to the production of the functioning carcinoid syndrome by bronchial or other extraportal carcinoids. In the case of pulmonary carcinoids without extraportal metastases, right-sided valvular heart disease would not be expected to occur. A systolic murmur was heard at the base of the heart in our case, but at necropsy the valves were normal.

Our thanks are due to Dr. K. Mattocks for the biochemical estimations, to Dr. V. J. McGovern for the necropsy report, and to Mr. Woodward-Smith for the photographic reproductions.

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HYPOTHERMIA AND THE HEART–LUNG MACHINE

CLINICAL APPLICATION OF THE TECHNIQUE

BY

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The concept of combining the heart–lung machine with hypothermia is by no means new. Many workers have combined a degree of hypothermia with their conventional heart–lung circuits, usually with the object of increasing their ability to handle larger patients.

A quite distinct development has been the use of a heart–lung circuit to achieve deep ranges of hypothermia. Notable in this field have been Gollan *et al.* (1955), who first reported extracorporeal cooling to 0° C. in dogs, and more recently there has been the experimental work of Kenyon and Ludbrook (1957). Drew and Anderson's (1959) clinical work has demonstrated the safety and advantages of temperatures around 15–20° C. The use of mechanical pumps in deep hypothermia is to maintain the circulation at temperatures below 30° C. At this temperature and below, the efficiency of the heart as a pump becomes progressively impaired until ventricular fibrillation supervenes.

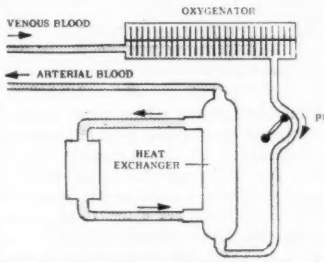

FIG. 1.—Diagram of the circuit used. In clinical use a coronary sinus reservoir and two suction pumps are added.

The use of moderate degrees of hypothermia with the conventional heart – lung machine adds a complication to the apparatus without fully exploiting the advantages of hypothermia. On the other hand, a deep or profound reduction of body temperature, while providing the theoretical ideals of a quiescent heart and dry operating conditions, is hardly applicable in every case in which open heart surgery is contemplated.

Hypothermia offers the possibility of lower flows and reduced priming volumes. In this way blood trauma can be diminished and the ever-increasing burden on the blood banks is relieved.

With the object of providing a more flexible instrument and technique, a hypothermic by-pass apparatus has been designed. It is equally applicable to children and full-sized adults, and provides for short or long periods of by-pass with complete arrest of the circulation if required.

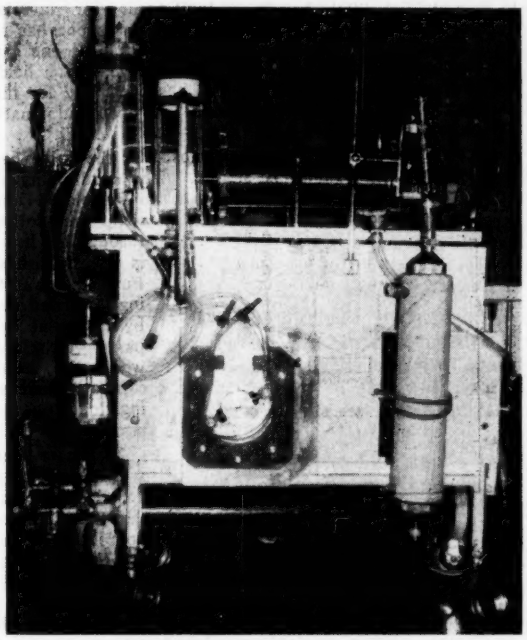

FIG. 2.—Photograph of the apparatus assembled for use.

Apparatus.—Basically the circuit consists of a disk oxygenator (rather smaller than the Kay–Cross variety) and a heat-exchanger made up of thin-walled stainless-steel tubes within an insulated casing (Fig. 1). The priming volume of the machine has been kept to a minimum, and is 3 pints (1.7 litres) for the average case. It is hoped to reduce this further. All blood spilt from the heart and operative field is returned to the circuit by two separate pump lines (Fig. 2). The disks normally rotate at 120 revolutions a minute, but a slower speed-setting is provided. Cooling and rewarming fluids at −4° C. and +45° C. respectively are supplied to the heat-exchanger by a conventional hypothermic apparatus.

Technique

As soon as the chest has been opened, the venae cavae and the femoral artery are cannulated simultaneously. Cooling is then started by a partial by-pass technique—it is in effect similar to the venous cooling method of hypothermia (Ross, 1954), but a proportion of the venous return is taken from the cavae, oxygenated, cooled, and returned to the femoral artery instead of to the venous system.

The initial cooling to 30° C. takes about five minutes. When the myocardium is beginning to flag and the body's metabolic requirements are down to about 50% of normal, the patient's heart is completely by-passed by tightening the vena caval snares. At this temperature it is easy to achieve what amounts to full physiological flows even in adults. A number of possibilities are now available as follows:

1. Further active cooling can be stopped, and a conventional by-pass is then carried out with the advantages of the reduced flow requirements and the added safety factor

of hypothermia should a technical fault occur—for example, a loose connexion. Under these circumstances one has at least 10 minutes of circulatory arrest available or one can deliberately arrest the circulation to achieve a dry field. This conventional by-pass at 30° C. has been used for the closure of atrial septal defects and for open pulmonary valvotomy (Fig. 3).

As soon as the septal defect is closed or the valve has been opened, rewarming is started. The cardiotomy is then closed and the circulation through the heart is re-established. Further rewarming is carried out by a partial by-pass technique while the heart carries an increasing load of the circulation.

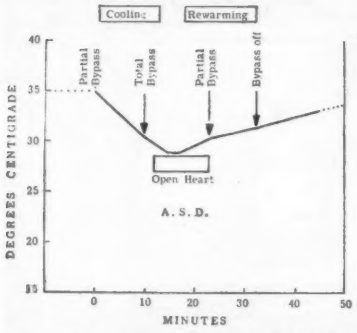

FIG. 3.—Temperature chart recorded during closure of an atrial septal defect in a 47-year-old woman.

2. Where one is dealing with a ventricular septal defect or a more complex lesion, say Fallot's tetralogy, partial by-pass cooling again proceeds to 30° C., at which stage the right ventricle is opened. While the infundibular resection is carried out, active cooling is continued to the region of 17-20° C. The ventricular septal defect can then be closed, with the advantage of a relatively quiescent heart. At this temperature, flows can be completely arrested as in Drew and Anderson's technique, but more often a very low (10 ml./kg.) flow has been used. This flow avoids the embarrassment of an excessive bronchial return and avoids a pressure build-up in the great veins. It is also likely that a partial cerebral flow is better than no flow at all even at these temperatures. To provide for this low flow a slower setting of the pump is calibrated and a slow rate of rotation of the oxygenator disks (30 r.p.m.) is maintained. Increased flows and rewarming are started as soon as the defect has been closed (Fig. 4).

3. In dealing with calcific aortic stenosis, up to an hour's work on the valve is sometimes necessary. During this time coronary flow has to be maintained with awkward perfusion techniques at normal temperatures. However, with the aid of deep hypothermia adequate protection is afforded to the myocardium, and the heart can be restarted without difficulty once the circulation is re-established.

4. In the case of complex anomalies like transposition of the great vessels it has been possible to cool to a very low temperature and to arrest the circulation completely for re-deployment of the caval cannulae. Even using total circulatory arrest, it is reassuring to have the ability to switch on a circulation at any stage and without delay.

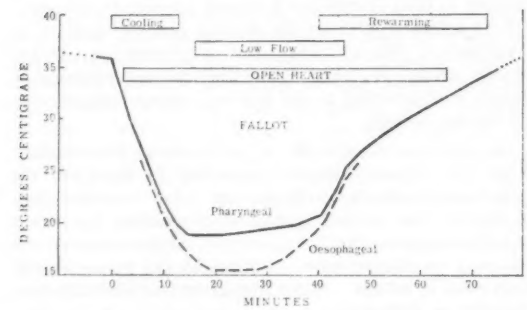

FIG. 4.—Fallot's tetralogy. The heart was open for about 60 minutes and the circulation was maintained on a low flow for 30 minutes at a temperature between 15 and 20° C.

Results

Twenty-five cases have been operated upon by me, though the machine and technique have been used on a number of additional patients. There has been no attempt to select the cases on the basis of age, weight, or type of lesion. Four of the six deaths were in bad-risk patients—two of these cases being reoperations for Fallot's tetralogy. One death was in a high-resistance ventricular septal defect (11 units), and one was a case of transposition. The two additional deaths were in a case of Fallot's tetralogy in which the septal defect reopened and in a case of calcific aortic stenosis where death resulted from a basilar artery embolus.

Ages have varied from 2 to 47 years and weights from 11 to 81 kg.

Summary

The method described aims at tailoring the needs of the patient to the capacity of a smaller machine. Low but physiologically full flows and low priming volumes are achieved. There is the added safety factor of hypothermia allowing for periods of complete circulatory arrest in case of mishap or where a dry field is essential.

Deep hypothermia permits operations on the aortic valve without the need for coronary perfusion methods.

The full range of hypothermia is available from moderate degrees of cooling to deep hypothermia, together with a circulation of oxygenated blood available in any quantity and at any stage during the procedure.

Total circulatory arrest has been avoided where possible. Instead, a low flow has been maintained in order to prevent rises of venous pressure and the accumulation of metabolites. Under these flow conditions there has been no need to combat metabolic acidosis, and recovery in all survivors has been gratifyingly prompt.

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The first car—a Morris Miniminor—has been issued under the Government's scheme to provide better transport for those war pensioners disabled in the service of their country who are eligible for Government-issued power-propelled tricycles. Cars have been available for some of the most severely disabled war pensioners since 1948, when a scheme was introduced by the former Ministry of Pensions. On March 31 last 1,802 war pensioners in the United Kingdom and Ireland had cars, but for other severely disabled war pensioners, not eligible for cars, power-propelled tricycles have been supplied, and the number of these issued in England and Wales at the same date was 1,577. Where cars are supplied the Ministry pays the insurance and road tax, and the pensioner gets an annual allowance towards maintenance. This allowance, which increases as the car gets older, averages £65 a year over the first eight years. There is also a grant towards engine replacement once during the pensioner's use of the car. If he cannot drive he may have a friend nominated to drive for him. The Ministry pays for the insurance, tax, and maintenance of Government tricycles. There is also an annual allowance in the case of power-propelled tricycles to compensate for the increases in petrol duty of 1951 and 1952.

STUDIES IN THE EPIDEMIOLOGY OF TINEA PEDIS

IV. SEED AND SOIL

BY

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Our survey of tinea pedis in day-school children in Bristol (English and Gibson, 1959a) showed that girls had a uniformly low infection rate, averaging 1.6%, while the average infection rate among boys was 6.6%, with a significant variation according to the district in which their schools were situated. This variation was associated with the degree of infection found on the floors of the local swimming-baths (English and Gibson, 1959b). Later it was shown that these children did not usually contract their infection in their homes (English and Gibson, 1960).

The present investigation attempts to throw some light on factors of "seed" and "soil" which could account for the foregoing observations.

The work of Vanbreuseghem *et al.* (1952) and Tritsmans and Vanbreuseghem (1955) suggested that the frequency with which swimming-baths were used might be of considerable importance in the epidemiology of the disease. We have therefore investigated the frequency with which the children swam at public baths and all other occasions on which they might go barefooted in places where infection could be contracted.

Strauss and Kligman (1957) have shown experimentally that moisture and warmth favour interdigital fungus infections, and common observation without, so far as we can find, strict mycological control supports this view. Therefore we have included in our survey a detailed study of the children's footwear.

The investigation was carried out in the same schools and, so far as possible, on the same children as the previous school survey, in order to obtain the greatest possible uniformity of conditions.

The Subjects

The children, who were between 11 and 15 years old, attended senior schools 1–12 of our first survey (English and Gibson, 1959a), which took place approximately one year before the present one. Children in their second, third, and fourth "school years," approximately 12, 13, and 14 years old, were chosen exclusively from pupils who had been seen at lower grades in the first survey. A few in their first year, approximately 11 years old at the time of the present survey, had been seen at the first survey while attending junior schools 13–16, and these were again chosen for this investigation; but most of the younger children were now seen by us for the first time.

Two groups of children were selected: in the first the footwear, swimming habits, etc., of infected and uninfected children were compared; in the second the same comparisons were made for boys and girls.

The first group consisted of 67 boys infected with tinea pedis at the first survey who were still at school, together with one control each—namely, the next uninfected boy on the class register.

At the first survey the *interdigitale* type of *Trichophyton mentagrophytes* had been isolated from 57 of the 67 infected boys, *T. rubrum* from 3, *Epidermophyton floccosum* from 4, and 3 had unidentified fungi. At the present survey 47 of the boys were cured; 19 were still infected with *T. mentagrophytes* and 1 with *T. rubrum*.

Only 12 girls who had been infected at the first survey were still at school. These were examined together with two controls for each—namely, the next two girls on the class register. The number of girls was even then too small for any conclusions to be drawn on factors affecting incidence.

The second group was composed of approximately equal numbers of boys and girls drawn from each of the four "school years" and chosen without any bias which would affect bathing habits and footwear.

Twelve boys and two girls of the second group of children were currently infected with *T. mentagrophytes* (*interdigitale* type).

The survey was carried out during 1958.

Methods

The same questionary was used for both groups and was prepared in such a way that the replies could be used for punched-card analysis without further coding. As well as questions concerning the children's footwear and bathing habits, the type and condition of the foot, and any occasions on which contact with the fungi could take place were also noted. Interviews were held in the schools, the questioning being mainly carried out by one of us (M. D. G.) with help from another (M. P. E.).

Scrapings were taken from the toe-webs of all children, including those with no lesions, by one of us (M. P. E.) and submitted to mycological examination by the methods of the previous survey (English and Gibson, 1959a).

The statistical planning of the survey and the analysis of the results were the responsibility of the third author (E. H. L. D.).

Terminology.—The words "bathed" and "bathing" here refer to "going for a swim" *not* to "taking a bath."

Results

Comparison of Infected Boys with Uninfected Controls from the Same Form

Footwear.—The footwear of the infected boys and controls was almost identical.

Bathing.—Table I shows that infected boys began to attend swimming-baths at a significantly earlier age than their controls, and had therefore been exposed to the risk of infection from this source for longer. Almost all boys, whether infected or not, bathed regularly with their school. This entailed at the most one visit to the baths per week during term-time and it was not possible to show any relationship between these visits and infection. However, many of the boys also went swimming out of school hours, and there was a statistically

TABLE I.—*Age at Which Bathing was Begun in Infected Boys and Controls*

Category	No. of Boys	Age in Years							
		Under 7		7–9		10 and 11		12 and Over and Non-bathers	
		No.	%	No.	%	No.	%	No.	%
Infected	67	9	13	28	42	23	34	7	10
Control	67	1	1	25	37	23	34	18	27

$\chi^2 = 11{\cdot}410$. Degrees of freedom = 3. $P < 0{\cdot}01$.

TABLE II.—*Use of Swimming-baths Out of School Hours by Infected Boys and Controls*

Season	Category	No. of Boys	Frequency of Use of Baths					
			More than Once a Week		Once a Week or Less		Never	
			No.	%	No.	%	No.	%
Summer	Infected	67	26	39	35	52	6	9
	Control	67	15	22	34	51	18	27
Winter	Infected	67	14	21	37	55	16	24
	Control	67	8	12	30	45	29	43

Summer: $\chi^2 = 8{\cdot}966$. Degrees of freedom = 2. $P < 0{\cdot}25$.
Winter: $\chi^2 = 6{\cdot}134$. ,, ,, ,, = 2. $P < 0{\cdot}05$.

significant relationship between incidence of infection and frequency of out-of-school bathing both in winter and in summer (Table II). It would therefore seem reasonable to suppose that frequent bathing and infection are related. Moreover, children bathing out of school hours would be using the baths at a time when adults, who are probably more highly infected, were swimming, and therefore would run more risk of acquiring a fungus infection.

Other Factors.—21 infected boys had crowded toes and three had widely spaced ones; eight controls had crowded toes and 12 had widely spaced ones. The association of infection with crowded toes was statistically significant ($P<0.05$). No significant difference was found between infected and uninfected boys in their use of school or other showers, in the frequency with which they went bare-footed or wore sports footwear without socks, admitted to exchanging footwear, or washed their feet. The degree of sweating of the feet was estimated by combining the boy's estimate of this with observation of the condition of his socks. No association was found between heavy sweating and infection. Strauss and Kligman (1957) produced really severe maceration artificially and noted that it was incompatible with fungal growth: Cremer (1959) has reached the same conclusion.

Comparison of the Habits of Boys and Girls

Footwear.—Table III shows that there is a considerable difference in the shoes worn by boys and girls, both in winter and in summer. Nearly 80% of boys wore lace-up shoes during some part of the summer, compared with only 8% of girls. Most girls wore either slip-on shoes (light leather shoes without laces or straps and often low-cut) or sandals. The usual alternative to lace-up shoes for boys was gymnastic shoes (canvas shoes with rubber soles), which are notorious for overheating the feet. In winter, boots of some sort were widely worn by both sexes; but while 62% of girls wore slip-ons as an alternative, 97% of boys wore lace-up shoes. In girls the choice between sandals and slip-on shoes in summer, and between lace-up shoes and slip-ons in winter, was largely determined by age, the older girls preferring slip-ons at both seasons. Striking differences between the hosiery fashions of boys and girls, especially in summer, are shown in Table IV; for 50% of girls discarded both socks and stockings during at least some part of the summer, whereas this practice was virtually non-existent among boys. The older the girl, however, the more continuously she tended to wear some sort of hose. Nylon socks were the most popular for both sexes in summer, but whereas the alternatives for girls were cotton socks or nylon stockings, boys more often chose woollen socks. In winter 76% of boys wore the latter compared with 31% of girls. The general picture given by these results is of the much lighter and cooler footwear worn by girls than by boys, especially in summer.

Bathing.—There was no significant difference in the age at which boys and girls first used swimming-baths, nor in the regularity with which they attended school swimming classes. However, as Table V shows, 25% of boys bathed more than once a week in their free time in summer, and 10% in winter, compared with 10% and 3% of girls; 42% of boys never bathed in winter compared with 60% of girls. These differences between boys and girls were statistically significant.

School Showers.—80% of boys to whom school showers were available used them regularly, compared

TABLE III.—*Comparison of Shoes Worn by Boys and Girls**

Shoes Worn in Summer					Shoes Worn in Winter				
Type of Shoe	Boys		Girls		Type of Shoe	Boys		Girls	
	No.	%	No.	%		No.	%	No.	%
Sandals	48	18	90	63	Gymnastic shoes	2	1	0	0
Gymnastic shoes	67	50	16	11	Lace shoes	131	97	65	46
Lace shoes	107	79	11	8	Gumboots	64	47	44	31
Gumboots	6	4	2	1	Fleecy-lined boots	2	1	50	35
Casuals (boys) or slip-ons (girls)	14	10	125	87	Other boots	9	7	3	2
					Total boots	69	51	90	63
Total children	135		143		Casuals (boys) or slip-ons (girls)	9	7	89	62
					Total children	135		143	

* The percentages in tables concerning footwear do not add up to 100 per cent because most children wore two or three different types.

TABLE IV.—*Comparison of Hose Worn by Boys and Girls*

Type of Sock or Stocking	Hose Worn in Summer				Hose Worn in Winter			
	Boys		Girls		Boys		Girls	
	No.	%	No.	%	No.	%	No.	%
Nylon socks	110	82	88	62	65	48	74	52
Cotton ,,	21	16	54	38	12	9	32	22
Woollen ,,	47	35	0	0	101	76	45	31
Other ,,	13	10	1	1	9	7	1	1
Nylon stockings	—	—	21	15	—	—	40	28
Usually no hose	0	0	30	21	0	0	1	1
Occasionally no hose	0	0	42	29	0	0	15	10
Always with hose	134	99	71	50	132	98	123	86
Total children	135		143		135		143	

The discrepancy in the totals of the "boys" columns is due to omissions in filling in questionaries.

TABLE V.—*Use of Swimming-baths Out of School Hours by Boys and Girls*

Season	Category	No. of Children	Frequency of Use of Baths					
			More than Once a Week		Once a Week or Less		Never	
			No.	%	No.	%	No.	%
Summer	Boys	135	34	25	69	51	32	24
	Girls	143	15	10	91	64	37	26
Winter	Boys	135	13	10	65	48	57	42
	Girls	143	4	3	53	37	86	60

Difference between boys and girls:
Summer: $\chi^2 = 10{\cdot}534$. Degrees of freedom = 2. $P < 0{\cdot}01$.
Winter: $\chi^2 = 11{\cdot}647$. ,, ,, ,, = 2. $P < 0{\cdot}005$.

with 38% of girls. The floors of the showers of four boys' schools and one girls' school were sampled by Gentles's (1956) method immediately after they had been used, although we had no knowledge of the level of infection in the children last using them. Only one dermatophyte colony (*T. mentagrophytes—interdigitale* type) was isolated.

Other Factors.—60% of girls claimed that they washed their feet daily, compared with 20% of boys, but the appearance of the girls' feet did not support their statements. It is possible that the girls were more aware than the boys of the frequency with which their feet *should* be washed, and replied accordingly rather than with the strict truth. We considered it advisable, therefore, not to pursue this point any further. 16% of boys had crowded toes compared with 23% of girls; 19% of boys had widely spaced toes compared with 11% of girls. Statistically, the girls' toes were significantly ($P<0.05$) more crowded than the boys. No other significant differences were found among those habits of the sexes which were investigated.

Discussion

School Showers

It was surprising that attempts to isolate dermatophytes from the concrete floors of five school showers produced only one colony, especially as for swimming-baths Gentles's method had been very successful in our hands. It must be observed, however, that almost all the indirect evidence obtained so far supports this result. In neither the first survey (English and Gibson, 1959a) nor the present one was any correlation found between infection and the use of showers by individual boys. Similarly, in the first survey there was no association between the infection rate in any school and the presence or absence of showers. The only contrary evidence is the far more consistent use of showers by boys than by girls, but there are sufficient other factors to explain in large part the different incidence of the disease in the sexes.

Our results here are completely at variance with those of Gentles and Holmes (1957) for miners. They found that where mines had pit-head baths there was a much higher incidence of tinea pedis among the men than in mines without baths. Gentles (1957) was able to isolate dermatophytes freely from the floors of pit-head baths. The explanation may lie in the different use made of showers by schoolboys and by miners. Schoolboys never use the showers more than three times a week, usually only once or twice, whereas miners use them daily: day-school boys are allowed only two or three minutes underneath and rarely wash systematically, whereas miners take time to scrub down, and their feet are often badly macerated and peeling (Gentles, personal communication). It has been pointed out, too, that we did not know the incidence of infection in the classes using the showers immediately prior to our visit. In addition, the infection rate in miners was very much higher (16% to 50% in pits with showers) than in any of our schools, where the highest level was 8.9%.

No doubt the use of showers has some small cumulative effect on the level of infection, but this would be masked by more important factors such as the use of swimming-baths, and would be demonstrable only in a much larger investigation than the present one.

Bathing and Footwear

The association we have shown for boys between duration and frequency of attendance at swimming-baths and the incidence of infection is in complete agreement with the work of Tritsmans and Vanbreuseghem (1955) on Belgian swimmers, and also confirms the observations of Amrein (1953) in Switzerland. Marples and Chapman (1959), on the other hand, found no association between swimming and infection in a mixed school of 387 children in New Zealand. They suggest that this may be due to their comparatively small numbers and low infection rate. But their "frequent bathers" went to the baths "at least once a week," whereas our keenest children went once a week with the school and more than once in their own time—that is, a minimum of three visits a week. The New Zealand school also had its own swimming-bath, and only some of the children ever visited the municipal baths and came into contact with adult bathers.

Because of the more qualitative nature of the evidence, the correspondence we have shown between type of footwear and incidence of tinea pedis in the sexes is suggestive but not conclusive. Scheffler (1958) and Marples and Chapman (1959) found an almost equal incidence of tinea pedis in boys and girls. Scheffler's results cannot be compared strictly with ours, as *T. rubrum* was of much more frequent occurrence in his subjects and its epidemiology may differ from that of *T. mentagrophytes* (English and Gibson, 1959a, 1960). In the New Zealand school, however, where *T. mentagrophytes* was the predominant fungus, woollen socks and gymnastic shoes were the favourite footwear for both sexes in winter, when the survey was carried out. Though no figures are available for the summer, it was observed to be common practice for girls to wear cotton ankle-socks while boys wore no socks, and for both sexes to wear gymnastic shoes or sandals (Marples, personal communication). In these children, therefore, the slight difference that exists between the footwear of the sexes should tend to favour a higher incidence in girls.

In observations on different communities, Davies (1951, 1952), Copland (1952), and Nickerson *et al.* (1945) show that a number of skin conditions of the foot, including tinea pedis, were exacerbated by raised temperatures and heavy footwear, but the work was not mycologically controlled. Doupagne (1957, and personal communication) found that tinea pedis occurred among Congolese soldiers wearing heavy boots and socks, but not among the native civilian population, who wore light socks and sandals or went barefooted. This observation is complicated, however, by the fact that the communal living conditions of the soldiers would, in themselves, undoubtedly be expected to increase the incidence.

This aspect of the epidemiology of tinea pedis has, however, been carefully investigated by Strauss and Kligman (1957) in their experimental work on a male prison population. In men with normal feet they were able, on 25% to 50% of occasions, to produce tinea pedis by occluding the toes on either side of massively inoculated interdigital spaces with a rubber condom, while in unoccluded, inoculated interdigital spaces infection was never obtained. On the other hand, the continuous wearing of a rubber boot for a week promoted infection in only one inoculated subject out of six. Similarly, when the normal interdigital spaces of men whose other toe-webs were naturally infected were occluded, the occluded spaces of five out of seven subjects became infected. The wearing of boots daily for up to a month also produced infections in three out

of five subjects under these conditions. Infection was never produced in toe-webs of uninfected feet similarly treated but not inoculated. The great majority of experimentally induced infections were spontaneously cured after the removal of the occlusive condom or boot, a foreseeable result, as the subjects must have included a number who were naturally resistant to the disease.

The experimental conditions in this work are obviously much more severe than the mere wearing of thick socks and shoes in hot weather by schoolboys, combined with intermittent exposure to small pieces of infected skin shed at swimming-baths and other places. On the other hand, the experiments were of comparatively short duration, while our schoolboys bathed several times a week and persisted in the use of unsuitable footwear for years on end. The relevance of our purely observational evidence of the great difference in the normal footwear of boys and girls, especially in summer, to the epidemiology of tinea pedis, does receive some support from these experiments of Strauss and Kligman.

Table VI summarizes and compares our results for both groups of children. Observations 1 and 2 are concerned with the exposure to infection of the children (" seed "); observations 3–5 would affect the suitability of the " soil " for the growth of this seed.

TABLE VI.—*Summary of Results*

Habit or Characteristic	A. Infected Boys and Uninfected Controls		B. Boys and Girls	
	Boys	Controls	Boys	Girls
1. Age of starting bathing	Early	Later	Moderately early	Moderately early
2. Spare-time ,,	Frequent	Moderate	Frequent	Moderate
3. Footwear in winter ..	Heavy	Heavy	Heavy	,,
4a. ,, ,, summer ..	,,	,,	,,	Light
4b. Socks or not	Always	Always	Always	Often without
5. Toe spacing	Tendency to crowding	Tendency to wide spacing	Tendency to wide spacing	Tendency to crowding

In section A, the infected boys had been exposed to greater risk than the uninfected by virtue of the frequency and long duration of their attendance at swimming-baths. But all the boys wore equally hot and heavy footwear. This suggests that where the soil in any group tends to be favourable for infection the actual infection rate will depend on the extent of contact with the inoculum.

In section B, where boys are compared with girls, there was less difference between risk of infection, for though girls swam less often than boys, they started just as early. On the other hand, there was a very striking difference in the footwear of the sexes, especially in summer, which might be expected to be the critical season (Strauss and Kligman, 1957). This could mean that where soil conditions are limiting these alone can keep the level of infection low. However, a complicating factor is that, simply because the infection rate in girls is so low, they never expose each other to as heavy an inoculum potential in their changing accommodation (English and Gibson, 1959b) as do boys. It will be noticed that though infected boys had more crowded toes than uninfected boys, girls, with a low infection rate, had more crowded toes than boys. This contradictory finding suggests that crowded toes are of importance in the epidemiology only when other factors are also favourable.

In this investigation we have been unable to take host resistance to tinea pedis into account because of lack of knowledge of the subject. That some persons of both sexes are resistant is a matter of common observation (Vanbreuseghem *et al.*, 1952 ; Baer *et al.*, 1955 ; Gentles and Holmes, 1957 ; English, 1957 ; Strauss and Kligman, 1957). That we have been able to demonstrate marked differences in the behaviour of infected and uninfected groups of children despite this would seem to add to the significance of our results. On the other hand, we have no proof that the different levels of infection in the sexes is not wholly or partially due to some resistance factor inherent in the female sex. This would be an interesting field for further work.

Summary

An attempt was made to study the infectivity of, and susceptibility to, tinea pedis in school children.

It was shown that infected boys started to attend their local swimming-baths at an earlier age than uninfected ones, and also used them more frequently. Most boys wore hot and heavy shoes and socks all the year round. The frequency and duration of the use of school showers was limited and no relationship could be shown between infection and their use.

In a group of boys and girls chosen without bias affecting their bathing habits or footwear there was no significant difference in the age at which bathing was begun, but boys bathed more often out of school hours. Girls' footwear was shown to be much lighter and cooler than boys, especially in the summer.

It is suggested that where, as in boys, badly ventilated footwear renders the feet a suitable soil for fungal growth the infection level in a community will depend on the extent of exposure to infective particles, the seed. On the other hand, the well-ventilated footwear of girls may be the limiting factor which keeps their infection rate low. The possibility of resistance in girls due to sex has yet to be investigated.

We wish to acknowledge the kindness of the head teachers and staffs of the schools in suffering a second visit from us. Our thanks are also due to Dr. J. C. Gentles, Professor R. Vanbreuseghem, and to Dr. G. A. J. Ayliffe for critical reading of the manuscript; and to Dr. R. P. Warin, Dr. C. D. Evans, and Professor R. C. Wofinden for encouragement throughout.

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STUDIES IN THE EPIDEMIOLOGY OF TINEA PEDIS

V. SOME DAY-SCHOOLS REVISITED

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Second visits have seldom been made to communities which have once been surveyed for tinea pedis, though Gentles and Holmes (1957) visited one of their collieries a number of times. Consequently, there is little information on changes in incidence over a period, either in the community as a whole or in individuals, and the resulting epidemiological picture is a somewhat static one.

Our first survey in Bristol day-schools (English and Gibson, 1959a) gave an estimate of the level of infection in the city's school children before attention had been drawn to it. That survey, and our second visit to the same schools (English *et al.*, 1960) to investigate the children's footwear and use of swimming-baths, could be expected to attract the attention of both teachers and pupils to the condition. Also, much of the reservoir of infection should have been removed if most of the cases found at these two surveys had been successfully treated. The improvement in the cleansing of swimming-bath A which followed our visit to it (English and Gibson, 1959b) should, too, have lowered the incidence of tinea pedis in schools which used it. We have therefore revisited certain of the schools to discover whether, in fact, any changes in incidence had occurred.

The Subjects

The survey was carried out during the autumn of 1958 and the spring of 1959, approximately two years after the first survey, and at similar seasons. Senior boys' schools 1, 2, 3, 4, and 6, and senior girls' school 8 (English and Gibson, 1959a) serving children aged approximately 11 to 14 were revisited.

Schools 2, 3, and 4 were comparatively small and almost all the third- and fourth-year children in them at this survey had been seen at the first, when in their first and second years respectively. In schools 1, 6, and 9, which were larger, only a proportion of the children were seen at either survey, so that about 25% of third- and fourth-year pupils at the present survey had not been seen in their first and second years at the first, though they had been in school at the time. Children in their first and second years at the present survey were all newcomers to their schools since our first visit.

The possibility of error in the results is introduced by the fact that 3.6% of boys with lesions from whom no fungus was isolated were being treated for clinically diagnosed tinea pedis at the time of our visit. But the experience of ourselves and of many other workers, with clinical diagnosis without laboratory confirmation, suggests that most of these boys were not, in fact, suffering from a fungal infection.

Methods

These were identical with those used at the first survey (English and Gibson, 1959a). Scrapings were taken only from children with lesions; cultures were made from all scrapings, and microscopical examination was also carried out where there was enough material.

Correction of Report on First Survey.—Our results were there given in terms of "age in years" of the children. This was inaccurate: they should have been in terms of "year in school." Children remain in senior schools for four years, but are moved up each year as soon after their birthdays as is convenient, not on them. Hence, for example, first-year children, though mostly 11 years old, will include some recent 12-year-olds. This in no way invalidates the results of the first survey, but might affect any comparison with one truly based on age in years. The appropriate correction in terminology has been made in the present article.

Infection

Incidence in Boys

Table I shows that the total incidence of infection in boys fell from 7.1% at the first survey to 5.5% at the present one, but the difference was not statistically significant. In first- and second-year boys taken alone, however, there was a significant ($P<0.01$) fall in incidence from 6.7% to 3.7%. The only significant ($P<0.05$) change in an individual school was a fall from 8.9% to 4.5% in school 1. In the first survey there was no significant difference between the incidence in any two schools using the same swimming-baths: in the present survey the difference both between schools 1 and 2 and between schools 3 and 4 was statistically significant ($P<0.05$).

The second survey showed a relationship between infection and the degree of exposure entailed by the use of swimming-baths in the boys' own time. In the present survey the children were not questioned about spare-time bathing, but a further analysis of the figures from the second survey are of interest. In schools 1 and

TABLE I.—*Incidence of Tinea pedis in Senior Schools Compared with that at the First Survey*

	District	School	First- and Second-Year Children (11–12 Years Old Approx.)				Third- and Fourth-Year Children (13–14 Years Old Approx.)				All Children			
			Total	Infected	% Infected	% Infected 1st Survey	Total	Infected	% Infected	% Infected 1st Survey	Total	Infected	% Infected	% Infected 1st Survey
Senior boys	A	1	160	6	3·7	8·9	131	7	5·3	8·9	291	13	4·5	8·9
		2	119	6	5·0	8·0	149	19	12·8	10·2	268	25	9·3	8·9
	B	3	169	7	4·1	7·7	143	2	1·4	3·9	312	9	2·9	5·9
		4	153	4	2·6	6·0	123	18	14·6	6·7	276	22	8·0	6·3
	C	6	160	5	3·1	3·2	149	6	4·0	7·7	309	11	3·6	5·3
		All	761	28	3·7	6·7	695	52	7·5	7·5	1,456	80	5·5	7·1
Senior girls	A	8	140	0	0·0	0·6	166	6	3·6	3·6	306	6	2·0	2·2

3, with a large fall in the infection rate between the first and third surveys, the second survey showed that 15% and 17% of boys respectively had begun to bathe by the time they were 7. But in schools 2 and 4, where the change in the infection rate had been slight, 25% and 33% respectively of the boys were going to the baths at that early age. That is, in schools with the least improvement more boys had been going to the baths from an early age. On the other hand, there was no association between the frequency with which boys went swimming and change of infection in the schools.

In district A, where there had been an improvement in the hygiene of the swimming-bath after our first survey, 35% of the boys in school 1, which showed a significant drop in infection, did not begin to bathe until they were 12 or over, and would not, therefore, have been to the baths until they were adequately cleaned. But this was true for only 18% in school 2, where the level of infection was still high.

Persistence of Infection.—Out of all the schools, 28 boys who were infected at the first survey were scraped at both subsequent ones. Of these, four were infected on all three occasions; four were clear at the second survey but reinfected at the third, two with the same fungus and two with different ones; and 20 were clear at the second and third, or at the third survey. A further 25 boys who were infected at the first survey and clear at the second were not scraped at the third because they had no lesions then: the chances that these boys were indeed still free from infection are high (English and Gibson, 1959a). Even taking into account the fact that about 25% of the boys seen in their third and fourth years in schools 1 and 6 at the present survey had not been seen at the first, it is obvious that most of the infections found in older boys this time were new ones: persistent infections were not a serious problem in individuals, though epidemiologically they may well be important.

The relationship of age to infection is not considered here, as it would undoubtedly be affected by the treatment of cases found at previous visits.

Symptoms.—All boys with lesions were asked whether they noticed itching or burning of their feet. Table II shows that, though symptoms were not confined to children with infections, there was a statistically positive ($P<0.01$) association between symptoms and infection. This was not nearly so marked as in the survey of Marples and Bailey (1957), carried out on older subjects.

TABLE II.—*Association of Symptoms With Infection in Boys With Lesions*

	No. of Boys Infected	% Infected	No. of Boys Clear	% Clear
Boys with symptoms ..	21	26·3	71	14·3
Boys without symptoms ..	59	73·6	426	85·7
Total	80		497	

Infection in Girls

In the first survey infection in six girls' schools averaged only 1.6%; in the present one it was still low —2.2% (Table I)—in the one girls' school examined. This school stood in the same grounds and served the same families as school 2, the most highly infected boys' school at both surveys. We consider this reasonable evidence of a consistently low incidence of tinea pedis in senior girls' schools in the city.

Lesions

Table III shows that both the incidence and the age distribution of lesions in boys were almost the same as at the first survey. There was again no relationship between the incidence of lesions and of infection in any one school. Lesions in the single girls' school rose from 30.7% to 48.2%, an increase for which we could find no explanation.

TABLE III.—*Incidence of Lesions in Boys Compared With First Survey*

Age-Group	Total Boys	Incidence of Lesions		% With Lesions at First Survey
		No. of Boys with Lesions	% With Lesions	
1st year	412	138	33·5	37·5
2nd ,, ...	349	135	38·7	37·6
3rd ,, ...	337	132	39·2	42·1
4th ,, ...	358	172	47·0	47·8
All ..	1,456	577	39·7	41·3

Mycology

Table IV shows the relative frequency of the occurrence of the dermatophyte species in the 86 mycologically positive cases. The distribution was very similar to that found at the first survey, the great majority of infections, including all those in the girls' school, being attributable to the *interdigitale* type of *Trichophyton mentagrophytes*. All the isolations of *Epidermophyton floccosum* were made in school 2, whence came five out of the seven obtained at the first survey.

TABLE IV.—*Incidence of Dermatophyte Species Compared With First Survey*

Fungus	Present Survey		First Survey
	No. of Cases	% of Total Cases	% of Total Cases
T. mentagrophytes	74*	85·8	83·5
T. rubrum	4	4·7	7·0
E. floccosum	6* (86*)	5·9	6·1
Microscopically positive only ..	5	5·9	4·4

* Three combined infections—*T. mentagrophytes* and *E. floccosum*.

Discussion

The marked reduction in incidence of tinea pedis in first- and second-year boys is difficult to account for, especially as the high incidence among older boys was not, in general, attributable to persistent old infections but to new ones. The improved hygiene in bath A might offer the explanation for schools 1 and 2, but would not cover schools 3 and 4, whose swimming-bath (B) had always been adequately cleaned. Further observations on the same group of schools might disclose other reasons for periodic fluctuations in incidence in an age-group.

Schools 1 and 2 both had the benefit of the improved hygiene at bath A, but this was reflected by a lowered infection rate only in school 1. One reason for this might be that, as well as the three surveys carried out in all the schools, school 1 had also been the subject of a number of preliminary surveys during which our methods were worked out. In consequence, it had become very conscious of the disease, and among the boys "athlete's foot" was a social stigma, lesions being promptly reported and thoroughly treated. The head of school 2 told us he had been unable to raise any interest in the condition in his boys.

The low incidence of persistent infections is in agreement with our previous findings in children infected with *T. mentagrophytes* (English and Gibson, 1960), but apparently contrasts with the situation in miners (Gentles and Holmes, 1957). However, the overwhelming number of infections in the pit revisited by these authors were due to *T. rubrum*, a species notorious for persistence. Of the five cases that did recover, four belonged to the minority of men who had been suffering from a *T. mentagrophytes* infection. The miners' infections were probably also more severe and of longer standing than those of the majority of schoolboys.

The infrequency of persistent infections in schoolboys would seem to invalidate the difference in age at which swimming was begun as an explanation of the fall in incidence in school 1 but not in school 2. For if infections acquired while the baths were inadequately cleaned had been quickly cured, the risk of their being passed on would be small. The lax attitude of the boys of school 2 can probably again be invoked in explanation. It is likely that their infections, other than those found by us at the first two surveys, would be treated only after they had existed for some time and had become annoying or severe; meanwhile the disease would have been passed on to others.

Summary

A survey of tinea pedis has been carried out in six local authority senior day-schools in Bristol, five boys' schools and one girls' school, all of which were similarly surveyed two years previously.

In general, little change was noticed in the incidence of lesions, infections, or fungus species, despite the fact that previous visits should have resulted in greater awareness of the condition in both staff and pupils.

However, of the two boys' schools using a swimming-bath in which adequate cleaning had been begun only after the first survey, the incidence in one had dropped significantly from 8.9% to 4.5%, while that in the other had remained at a high level. This is attributed partly to the fact that 35% of boys of the first school had never been to the baths in their poorly cleaned state, compared with 17% in the second; and partly to the fact that "athlete's foot" had become a social stigma in the first school but not in the second.

Out of 53 boys infected at the first survey, 45 were clear at the present one. Persistent infections are not, therefore, a problem in individual boys, though epidemiologically they may well be important.

We are indebted to the head teachers and staffs of the schools for allowing us to visit them for a third time. Our thanks are due to Miss E. H. L. Duncan, of the Central Health Clinic, Bristol, for statistical help; to Mr. G. A. Wills for technical and clerical assistance; and to Dr. R. P. Warin, Dr. C. D. Evans, and Professor R. C. Wofinden for their interest and encouragement.

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COMPARISON OF POST-OPERATIVE PAIN AND STIFFNESS AFTER THE USE OF SUXAMETHONIUM AND SUXETHONIUM COMPOUNDS

BY

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Muscular pain and stiffness after the use of short-acting relaxants of the depolarizing variety is a major problem after dental in-patient anaesthesia. A clinical trial has been undertaken to compare the incidence of muscular pain and stiffness after the use of suxamethonium and suxethonium compounds.

Technique

The main investigation was carried out on 100 in-patients. The operative procedures were of the standard in-patient variety—namely, routine oral surgery and plastic operations about the mouth.

Anaesthesia was induced routinely by the intravenous injection of sodium thiopentone in a dose of 150–300 mg. Intubation was facilitated by the use of a short-acting relaxant, after which anaesthesia was maintained by means of nitrous oxide, oxygen, and halothane. The two relaxants chosen for comparison were suxethonium bromide in a dose of 180 mg. and suxamethonium chloride, dose 50 mg.; the use of bromide salts in place of the chloride has been shown to be irrelevant to the incidence of stiffness (Leatherdale, 1959). Each of us used the relaxants alternately on his own lists; both drugs were in the form of the ready-prepared solution.

The patients were admitted for a three-day period. For the first 24 hours after the operation they were confined to bed, after which they were ambulant. The ward sister, who was unaware of the relaxant used, kept a detailed record of pain and stiffness, and on discharge the patients received a form, which subsequently allowed us to follow their symptoms until they abated. From these records the accompanying Table has been compiled.

Summary of Results

Main Trial (100 Patients)	Severe Stiffness or Pain	Mild Stiffness	Total Incidence of all Types of Stiffness
Suxamethonium series (50 patients) ..	13	25	38
Suxethonium ,, (50 ,,) ..	13	20	33
Total ..	26%	45%	71%
50 female patients	16	28	44 (88%)
50 male ,, ...	10	16	26 (52%)
Series of Morris and Dunn (1957) ..	22%	50%	72%

Comment.—No significant difference existed in the incidence of pain and stiffness with the two compounds, and the overall incidence agrees well with figures given by Morris and Dunn (1957). Each series of 50 in the main trial comprised 23 male and 27 female patients, and by continuing recording after the initial 100 cases it

was possible to compare the sex incidence with 50 male and 50 female cases. As in previous surveys (Hegarty, 1956; Leatherdale *et al.*, 1959) female patients showed a higher incidence of symptoms.

Character and Duration of Stiffness

The character of the stiffness was not influenced by the relaxant used. The distribution was as follows: neck 59%; abdomen, 33%; chest, 31%; back, 10%; shoulders, 9%.

The onset was normally 12–24 hours after the operation, and only two patients developed symptoms later than 24 hours post-operatively.

In one-third of the patients the pain or stiffness had already recovered by the time they were due for discharge from hospital. In the others it lasted an average of one and a half days after discharge or four days in all. In only three patients did it persist for longer than five days after operation.

On completion of the cases analysed above, recording was continued on a control series, using gallamine as the relaxant for intubation. A further 25 cases were observed and only one case of mild transient stiffness was recorded.

Discussion

Foldes *et al.* (1956) showed that the duration of apnoea after 1.2 mg. of suxethonium per kg. body weight was shorter than that after 0.6 mg. of suxamethonium per kg. In our experience, even a dose of 180 mg. of suxethonium sometimes failed to give a satisfactory relaxation for intubation as 50 mg. of suxamethonium. With this dosage, the difference appeared to be in the intensity rather than duration of the paralysis.

The article by Enderby (1959) appears at first sight to contradict our results. He found a marked reduction of incidence and severity of stiffness after the use of suxethonium. However, the conditions in his series are not comparable to ours in that he used a small dose of suxethonium (50 mg. in his main series) to potentiate the action of decamethonium in patients requiring a hypotensive anaesthetic technique. A comparison of his results with our own suggests that the incidence and severity of stiffness may vary with the dose of relaxant.

Although there is the ever-present danger of a mixed block, a small dose of curare or gallamine given before suxamethonium reduces the incidence of stiffness (Churchill-Davidson, 1954; Morris and Dunn, 1957). These drugs antagonize the action of suxamethonium (Foldes *et al.*, 1957), probably by a competitive blocking action, so that they, too, may reduce post-operative stiffness by lowering the effective dose of depolarizing relaxant acting at the neuromuscular end-plate.

In our series we have endeavoured to include all forms of stiffness, and the symptoms recorded varied greatly from transient myalgia to true pains lasting five days. The incidence reported will depend upon the criteria used in assessment, and this may explain the varied results reported in previous series, representative figures being 36.4% (Leatherdale *et al.*, 1959), 72% (Morris and Dunn, 1957), 25.6% (Hegarty, 1956), 66.7% (Foldes *et al.*, 1956), 0% (Ruddell, 1957). Very rarely did any patient complain of symptoms directly to us, and we believe they were generally regarded by the patient as the usual "aches and pains" expected after an operation. This factor may elucidate the apparent absence of this complaint in the experience of some anaesthetists, especially after a major abdominal surgical procedure, when the patient may be suffering considerable pain from the site of the operation.

Summary

Suxamethonium chloride was compared with suxethonium bromide in a series of patients undergoing dental operations.

No significant difference in the incidence or character of the post-operative pain or stiffness was recorded.

We thank Dr. Victor Goldman for his help and encouragement in the production of this paper. Special thanks go to Sister J. Simmonds, of the Royal Free Hospital, for her help in recording the patients' symptoms.

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Medical Memoranda

Intraperitoneal Haemorrhage from a Vessel on the Surface of a Uterine Fibroid

Intraperitoneal haemorrhage from a vessel on the surface of a uterine fibroid is a rare complication. Barely 60 cases have been recorded in English literature.

The condition is of importance to the general surgeon as well as to the gynaecologist because the onset is sudden, producing acute abdominal symptoms, which may sometimes be referred to the epigastrium. The recorded pre-operative diagnoses have varied from ruptured ectopic gestation, haemorrhage from an ovarian cyst, twisted ovarian cyst, acute appendicitis, perforated gastric ulcer, intestinal obstruction, acute pancreatitis or ruptured spleen, to torsion of a pedunculated uterine fibroid. Very seldom has the diagnosis been made before laparotomy.

CASE REPORT

A married woman aged 33 experienced sudden severe lower-abdominal pain while sitting watching television. The pain became generalized and was very severe for three-quarters of an hour, but then was less severe unless she moved. Faintness and nausea developed, but no vomiting, shoulder pain, or diarrhoea.

Her last menstrual period had started six days earlier and was normal in amount, lasting four days. She had a regular 28-day cycle and did not think that she was pregnant. She was a para-1, with one miscarriage, and gave a history of occasional attacks of abdominal pain and vomiting for a few months before admission, but of no other illnesses.

On admission to hospital, four hours after the onset of pain, she was very pale and kept feeling faint; temperature 97° F. (36.1° C.), pulse 92, and blood-pressure 95/60 mm.

Hg. There was no secretion in the breasts. The abdomen was slightly distended below the umbilicus but no mass was palpable. Tenderness and resistance were present in the lower abdomen, and it was not dull to percussion. On vaginal examination the cervix was slightly softened, but the body of the uterus was not clearly defined because of the abdominal resistance. An extremely tender indefinite mass was felt in the right fornix and she was very tender in the pouch of Douglas and experienced pain on movement of the cervix.

A provisional diagnosis of ruptured ectopic gestation or haemorrhage from a follicular or endometriotic cyst of the right ovary was made.

Blood was taken for cross-matching, and an intravenous drip of 1 pint (568 ml.) of dextran was started, followed by 3 pints (1,704 ml.) of blood.

At laparotomy about 1½ pints (852 ml.) of fluid blood and clots were removed from the peritoneal cavity. Both tubes and ovaries were normal. The uterus was enlarged by a subserous uterine fibroid about 2 by 2½ in. (5 by 6.2 cm.), situated on the right side of the anterior surface of the uterus just below the right cornu. On the surface of the fibroid were several thin-walled veins, one of which had ruptured and was bleeding freely. There were no adhesions around the uterus.

Myomectomy was performed and the uterine wall closed. The fibroid was very superficial in the uterine wall, and the resulting scar was only about 1 in. (2.5 cm.) long.

The patient had a post-operative respiratory infection, but otherwise made an uneventful recovery.

The pathologist reported a fibromyoma measuring 6 by 5 cm., containing haemorrhages. Microscopical examination revealed areas of oedema and thrombosis.

COMMENT

The cause of haemorrhage from a vein on the surface of a fibroid is not known, but Hasskarl (1949), in a review of the literature on 50 cases, states that most have followed a blow on the abdomen, a fall, or heavy work. His patient had been gardening and was menstruating when the pain started. McNeil (1952) was also of the opinion that sudden exertion might precipitate haemorrhage, especially during menstruation, when congestion might be present. His patient was menstruating and she had been hanging pictures when bleeding started. The fibroid was situated posteriorly, and had adhesions. Davies (1950) records two cases in which patients were sitting quietly at the time of intraperitoneal haemorrhage, though they were menstruating.

It seems to be more common for haemorrhage to occur when the fibroid is situated on the posterior wall of the uterus, for three of the above cases were thus situated, and so also was one of the two recorded by Shelfo (1939) and in each of those recorded by Schneider and Jemerin (1942), Woodruff (1948), and Sheehan (1951). However, fundal fibroids were present in Shelfa's other case and in those described by Bosch, Carter, and O'Grady (1950) and by Kaye and Ficarra (1950). One large fibroid on the anterior wall up to the umbilicus was reported by Li and Braden (1952); the woman was travelling by bus when her haemorrhage started. The case recorded here, however, had only a small fibroid situated on the anterior wall of the uterus, with no adhesions, and she was at rest and was not menstruating, so no precipitating factor seemed to be present, leaving the aetiology obscure. The age of the patients varied from 24 years (Goldstine, 1921) to 52 years (Shelfo, 1939).

In most recorded cases treatment has been by some type of hysterectomy, though simple ligation of the bleeding vessel was reported in one case in Hasskarl's review. He recorded treatment by myomectomy in 12 cases, and to these may now be added Sheehan's case and the present one. Myomectomy seems the only justifiable treatment in young patients, particularly when few fibroids are present and they are readily accessible. Blood transfusion is, of course, required in the majority of patients, as haemorrhage is severe.

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Hypertrophic Osteoarthropathy Associated with Carcinoma of Stomach

The subject of hypertrophic osteoarthropathy was first brought to the attention of the medical world by Bamberger (1889) and Marie (1890). Suppurative pulmonary conditions such as bronchiectasis, empyema, lung abscess, and tuberculosis were regarded as the chief aetiological factors, but now, with the changing pattern of pulmonary diseases, bronchogenic carcinoma is gradually emerging as the principal primary disease responsible for arthropathy (Semple and McCluskie, 1955; Shapiro, 1956). Besides pulmonary and pleural diseases, hypertrophic arthropathy has been described, rarely, in congenital heart diseases, chronic gastro-intestinal diseases such as the sprue syndrome and ulcerative colitis, hepatic cirrhosis, and carcinoma of the nasopharynx. It is extremely rare to have osteoarthropathy associated with cancer of the oesophagus, and one such case has been described in which the malignant tumour developed as a complication of achalasia and was associated with marked features of hypertrophic osteoarthropathy due to pleural extension of the growth (Peyman, 1959). So far as we are aware, hypertrophic osteoarthropathy has not been described associated with carcinoma of stomach, and therefore the following case merits description.

CASE REPORT

A married labourer aged 46 was admitted to hospital in June, 1959, with the complaint of gradually progressive difficulty in swallowing, first with solids and later with fluids. He had lost a great deal of weight and was becoming progressively weak. There was no history of haematemesis. He also complained of a vague ill-defined pain in the lower chest on both sides. He was conscious of the fact that his wrists and ankles had greatly thickened during the previous six months and the finger-ends had become peculiar. His attention was directed to these changes by a constant dull ache in the wrist- and ankle-joints.

On examination he looked pale and ill-nourished. The face had an acromegaloid appearance with a large, shiny,

and bulbous nose. The nails and toes showed gross clubbing, and there was an obvious enlargement of wrists and ankles on both sides. The fingers were long and had a drumstick appearance. The nails were beaked and curved in all directions, exhibiting the so-called "watch-glass deformity." The spleen was enlarged to 4–5 cm. below the costal margin, and the liver by 1.5 cm. There was no palpable mass in the abdomen or any lymph-node enlargement in the neck. No clinical abnormalities were found in the respiratory or cardiovascular system except a grade 2 haemic systolic murmur.

FIG. 1.—Barium study of the oesophagus and upper end of the stomach, showing a large filling defect due to the growth and marked dilatation of the oesophagus.

Investigations. — Hb, 10.5 g.; R.B.C., 3,500,000 / c.mm.; M.C.V., 85.7 cubic microns; M.C.H., 30 $\mu\mu$g.; M.C.H.C. 35%; W.B.C. 15,000, with 64% neutrophils. E.S.R., 84 mm. first hour, Westergren. The routine urine analysis and stool examination were within normal limits. Barium study of the gastro-intestinal tract revealed a large growth involving the lower end of the oesophagus and upper end of the stomach (Fig. 1). Radiological examination of the wrists and ankles showed typical changes of hypertrophic osteoarthropathy (Fig. 2). Radiography of the chest showed nothing abnormal. Liver-function tests: serum bilirubin, 1.5 mg.; thymol turbidity, 1 unit; thymol flocculation ±; total proteins, 6.4 g.; albumin:globulin ratio 1.2: 1. Liver biopsy revealed normal hepatic architecture. Splenoportal venography did not reveal any evidence of portal hypertension or of intrahepatic obstruction.

Owing to progressive dysphagia, preliminary gastrostomy was performed, followed by the excision of a large growth involving the upper third of the stomach and the lower 2½ in. (6.5 cm.) of the oesophagus. The histopathological examination of the growth confirmed it to be an adenocarcinoma of the stomach. The patient's condition deteriorated suddenly two days after the operation, and he died. Permission for necropsy was not granted.

FIG. 2.—Radiograph of the wrists, showing evidence of periostitis and arthropathy along the distal ends of radius and ulna.

COMMENT

Hammarsten and O'Leary (1957), reviewing 91 cases of hypertrophic osteoarthropathy described since 1938 in the English literature, found that 79 were associated with pulmonary neoplasm and only 12 with other diseases, including empyema, tuberculosis of bones, sprue, leukaemia, myxoedema, and lung abscess; one appeared as an independent phenomenon. Peyman (1959) also stressed the rarity of hypertrophic osteoarthropathy associated with diseases of the oesophagus, and in the case described by him arthropathy had evidently followed the pulmonary invasion of the growth. In our case there were well-marked changes of osteoarthropathy associated with carcinoma of the stomach. There was no radiological evidence of the extension of growth into the lungs or pleura, and no such involvement was detected at operation. The osteoarthropathy had developed simultaneously with the onset of dysphagia, and was responsible for the pain and limitation of movements.

The pathogenesis of osteoarthropathy remains obscure. It is generally agreed that the malignant growth produces some primary metabolic aberration which may be mediated by some humoral mechanism or by autonomic pulmonary systemic vascular reflex. Such a theory could best explain the rapid relief obtained in the symptoms of arthropathy even a few hours after the resection of the growth, and may also explain the therapeutic efficacy of ligation of the pulmonary artery, hilum denervation, vagus resection, or removal of the tumour. Such hypotheses have been advocated only in relation to the carcinoma of the bronchus, but the association of arthropathy with the malignancy elsewhere, as in the case under review, indicates that similar changes may occur, due to a local growth anywhere else.

We are indebted to Dr. G. S. Sekhon for the operative treatment and to Dr. S. D. Khanna for the histopathological report.

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"We enjoy the artlessness of children. They endear themselves to us by being unaware of the humour of their words. But we do not look for the same quality in men of science, and the doctor who cannot understand why people are laughing at his words has lost some professional prestige, which is a necessary part of his stock-in-trade. 'The patient complains of tiredness after games of 8 years duration' was not a statement that would mislead many, but it made it harder thereafter to take that student seriously; which was a pity. So also for 'mucosal membrane in good shape,' 'I uncle paralised like him on Father's side,' 'he was given a reading correction to wear for 6 months,' '6 children 1 still born. All married'—and so on. The quality of naivety, present in these and many other examples, implies a lack of self-criticism: the writers could not detach themselves from their words, so as to hear themselves speak, or read with objectivity what they had written. And criticism—not least of oneself—is the basis of reason and science." (Dr. Geoffrey Rose, "A Learned Profession?", *St. Mary's Hospital Gazette*, June, 1960.)

Reviews

THYROID BULLETIN

British Medical Bulletin. Volume 16, No. 2. The Thyroid Gland. (Pp. 89–174; illustrated. 20s.) London: British Council Medical Department. 1960.

This, in the words of Sir Charles Harington, who has written the introduction, is an attempt to review the aspects of the subject in which advances have been most striking in the past ten years. The most conspicuous advances have been achieved by relatively new techniques such as chromatography and the use of radioactive isotopes, especially those of iodine.

Because its object is to review recent advances, it is inevitable that the *Bulletin* should be a little scrappy, but to avoid this fault the editor would have been forced to cast his net much wider and to have produced a number of unwieldy size.

The laboratory aspect is well covered; Dr. I. Doniach writes on types of thyroid growth, Dr. Rosalind Pitt-Rivers on the biosynthesis of thyroid hormones, Dr. Purves and Dr. Adams on T.S.H., Dr. Tata on the transport of thyroid hormones, and Dr. Brown-Grant on the hypothalamus and the thyroid. More practical chapters have been written by Dr. Trotter on deafness with thyroid dysjunction, by Mr. Selwyn Taylor on the genesis of the thyroid nodule, by Dr. Goolden on the diagnostic use of radioactive iodine, by Dr. McGirr on goitrous cretinism, by Dr. Clements on natural goitrogens, and by Dr. Kitchin and Dr. Evans on genetic factors. Dr. Eayrs discusses the influence of the thyroid on the central nervous system, and there are excellent topical reviews by Dr. Boyd and Dr. Oliver on plasma lipids, and by Dr. Roitt and Dr. D. Doniach on auto-immunity.

One misses a little any review of recent changes in the treatment of thyrotoxicosis, and what is said is not invariably accurate. Few practising physicians would agree that the use of isotopes "gives a measure of therapeutic control that is truly astonishing." Cancer of the thyroid goes almost without mention. A review of present knowledge of hypothyroidism would have been a useful additional chapter, despite the fact that a lot of the new work is to be found here and there in different chapters.

But these are minor criticisms of an excellent issue produced at a most appropriate time, the summer in which the Fourth International Goitre Conference is being held in London.

RAYMOND GREENE.

THE OUTCOME OF SCHIZOPHRENIA

Differential Treatment and Prognosis in Schizophrenia. By Robert D. Wirt, Ph.D., and Werner Simon, M.D. (Pp. 198 +xii. 50s.) Springfield, Illinois: Blackwell Scientific Publications. 1959.

The course of psychiatric illness is usually so long and the variables so many that the objective evaluation of any therapy is notoriously difficult. A method of treatment is often obsolete before it has been adequately evaluated. Insulin-coma therapy, for example, has been used for some 20 years, but there are still heretics who argue that most of the papers published about its therapeutic effects are poorly controlled and inconclusive.

In a similar way, though there are hundreds if not thousands of papers about the use of chlorpromazine and reserpine in schizophrenia, few of these stand up to critical examination, as the present authors show. They seek to remedy this deficiency by the "only research of its kind to include multidisciplinary evaluations by psychiatric examination, psychometrics, and social work techniques." Briefly, 80 schizophrenics, not previously treated, were placed in four groups of 20. One, the "Clinical Judgment" group, received whatever treatment seemed indicated according to the psychiatrist's clinical judgment; one received chlorpromazine, one reserpine, and the "Hospital Routine group" had all the facilities of the hospital, but no specific somatotherapy. The patients' progress was minutely assessed after 30 days and after a year by psychiatric, psychometric, and social efficiency ratings. The conclusions were that chlorpromazine is nearly as effective as the more complex traditional therapies such as insulin coma, E.C.T., or psychotherapy. Reserpine, on the other hand, was no better than giving no treatment beyond hospitalization.

This is certainly a very careful and elaborately reported study which compares favourably with most published work on the subject. It also reinforces the above statement about the difficulties of research, in that even such a complex study has inadequacies. We may know the value of chlorpromazine administered for 30 days, but there are many authorities who argue that it needs to be given for a much longer period to have therapeutic effect. Moreover, though chlorpromazine is not yet obsolete, it is being replaced by other phenothiazines such as trifluoperazine and perphenazine, the superiority of which over chlorpromazine is generally recognized.

A. W. BEARD.

POISON IN PRACTICE

Clinical Toxicology. By C. J. Polson, M.D.(Birm.), F.R.C.P., M.R.C.S., and R. N. Tattersall, O.B.E., M.D.(Lond.), F.R.C.P. (Pp. 589+xi. 42s.) London: English Universities Press, Ltd. 1959.

Among the many publications on the subject of toxicology this book is unusual in dealing especially with two of its aspects—poisons used in the home, and the legal obligations on the doctor involved in any case of poisoning. Since one of the authors is a barrister it is not surprising that the legal position is described in a manner which cannot fail to provide essential and accurate guidance for the medical practitioner and also the industrial physician.

Strong emphasis is laid on the frequent, sometimes fatal, effect of accidental swallowing of poisons commonly used in the home, and the information is given so clearly and concisely that it can be understood by those who have little knowledge of technical and scientific terms. It gives a much-needed warning that such poisons should be clearly labelled and kept in a safe place. The fatal results of using sodium nitrite in mistake for common salt, of drinking eyedrops or belladonna liniment from the wrong bottle, or of nicotine insecticide in mistake for whisky, are but a few of the examples of such negligence.

The chapter dealing with the general treatment of poisoning is of great value; even the technique of gastric lavage, a procedure which requires some experience, is described with great detail. The treatments for specific poisons are equally clearly described, with accounts of recent developments in therapeutic procedures. An example of the detailed practical instruction given is the

inclusion of the telephone numbers of institutions which can supply a specific antitoxin for the poisonous mushroom *Amanita phalloides*.

The actual case histories, of which there are many, make fascinating reading for anybody addicted to crime literature, with many interesting if perhaps sometimes slightly irrelevant details of the personalities concerned, such as Mary Blandy, a parricide who used arsenic, and who was described in 1752 as "an emblem of chastity and virtue, graceful in person, of mind elevated."

Some of the better-known industrial poisons are described, and here again the case histories are valuable in giving a picture of the varied clinical manifestations. But this book is not primarily a textbook of industrial toxicology, and no attempt has been made to give a comprehensive account of every toxic substance encountered in industry. It is essentially a most readable volume which can be studied with profit and pleasure not only by the medical profession as a whole but also by a large section of the general community.

ETHEL BROWNING.

LYMPHOMAS AND THE SKIN

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, B.S., M.D., F.A.C.P. Introduction by Steven O. Schwartz, M.D. (Pp. 534+xiii; illustrated. £6 4s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This book deals with the skin manifestations of mycosis fungoides, Hodgkin's disease, and lymphosarcoma. Much of the text is made up of exhaustive quotations and references to the literature—there are, for example, 378 references given to mycosis fungoides—and rather close reading is required to discern the general pattern amid the abundance of detail. The author maintains that, when so-called mycosis fungoides starts with cutaneous tumour formation (which he refers to as the *d'emblée* form) it is always lymphosarcoma and never mycosis fungoides; though this often proves to be so it is probably not generally accepted. With this exception the views the author expresses as his own are not unorthodox. They are given without undue emphasis and the conflicting opinions of others receive full consideration. The reader is thus left to form his own conclusions, and all through the book there is a striking absence of dogmatism. For the student or beginner this may be confusing, but for the dermatologist, and more especially for the general physician, the book is one to which he may turn with profit both for guidance in the practical diagnosis and management of patients, and also as a splendid starting point for more extensive reading.

Dermatologists and general physicians would do well to obtain this book or to make sure that they have ready access to it.

F. RAY BETTLEY.

IS CANCER HEREDITARY?

Cancer in Families. A Study of the Relatives of 200 Breast Cancer Probands. By Douglas P. Murphy, M.D., and Helen Abbey, Sc.D. (Pp. 76+x. 20s.) Cambridge, Mass.: Harvard University Press (Commonwealth Fund). London: Oxford University Press. 1959.

The extent to which cancer can be regarded as a hereditary disease has long been under debate, and very different opinions continue to be expressed. This is somewhat surprising, as the question is not intrinsically difficult and the answer is of considerable practical importance. The uncertainty may, perhaps, be attributed to the apparent contradiction between the results obtained from observations on pure lines of experimental animals and those obtained from human families. It has, however, been accentuated by a lack of uniformity in the human data. All recent studies agree in showing that cancer is certainly not much commoner among the relatives of cancer patients than among the relatives of control subjects not suffering from cancer, but some have suggested that the frequency of cancer of the same site as that observed in the propositus is several times greater in the cancer families. This difference is most reasonably attributed to a difference in the techniques employed, and particularly to the fact that all the studies have had to rely largely on knowledge and memory of events which happened many years before the inquiry was begun.

In the study reported by Professor Murphy and Professor Abbey it was hoped to reach a definitive answer by obtaining the information directly from each member of the family group or from a first-degree relative. This entailed an enormous amount of work, and although only 398 families were studied (200 families of breast-cancer patients and 198 families of control patients attending a dental clinic) four interviewers were employed on the work for over six years. Altogether 11,635 relatives were traced (parents, sibs, uncles, aunts, and first cousins), and 1,678 of them were interviewed in person. With one minor exception, no evidence was found of any difference in the incidence of cancer in the two groups nor was there any significant difference in the incidence of the specific type of cancer with which the propositi were afflicted. All who are interested in the causes of cancer will need to read this book to judge for themselves the reliability of the evidence. In my opinion the families are shown to have been properly comparable and the evidence is good, but the small numbers of cases of breast cancer among first-degree relatives will prevent the results from outweighing the positive findings of other investigators. Nevertheless, this is an important study, and it is most valuable to have the detailed results set out fully and clearly.

RICHARD DOLL.

RADIOTHERAPY FOR TRAINEES

A Short Textbook of Radiotherapy for Technicians and Students. By J. Walter, M.A., B.M.(Oxon.), M.R.C.P. (Lond.), F.F.R., D.M.R.E.(Camb.), and H. Miller, M.A., Ph.D.(Camb.), F.Inst.P. Second edition. (Pp. 527+xi; illustrated. 56s.) London: J. and A. Churchill, Ltd. 1959.

This book is addressed primarily to student technicians working for the examinations of the Society of Radiographers. However, the first edition, which admirably fulfilled this aim, rapidly became a favourite also with candidates for the radiotherapy diplomas. The authors, in the second edition, have brought the work thoroughly up to date, so that more recent developments in the fields of megavoltage therapy, medical uses of radioactive isotopes, hormone therapy, and radiomimetic agents are now adequately covered; there are excellent introductory chapters on physics and technics, and a brief though remarkably informative and lucid chapter on the biological effects of radiation. Altogether, this is an excellent book, and will assuredly retain its popularity with trainee technicians and radiotherapists.

W. M. LEVITT.

ADOLESCENT RORSCHACHS

Adolescent Rorschach Responses. Developmental Trends from Ten to Sixteen Years. By Louise Bates Ames, Ph.D., Ruth W. Metraux, M.A., and Richard N. Walker, Ph.D. (Pp. 313+xiii. 63s.) New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers. London: Hamish Hamilton, Ltd. 1959.

This book is a sequel to an earlier volume by the same authors, entitled *Child Rorschach Responses*, and bridges part of the gap between that book and one on *Rorschach Responses in Old Age*. It reports the analysis of 700 Rorschach records taken from 50 boys and 50 girls each at ages 10 to 16, and the main purpose of the study has been to determine developmental trends in Rorschach responses. In order to do this descriptive statistics have been computed for the two sexes separately at each age, making use of the usual Rorschach scoring variables. Distributions have also been tabulated for a number of additional "qualitative" variables, such as "the semantics of identifying concepts, the types of adjectives used, the initial exclamations given." Particular attention has been paid throughout to sex differences, which have been summarized and described by the authors. Descriptive sketches are given of the "typical" Rorschach responses at each age level.

This book will be evaluated quite differently by those who are convinced of the value of the Rorschach test, and by those who are familiar with the large literature on the experimental analysis and validation of the test which, on the whole, has been strongly negative in its conclusions. On the positive side, it may be said that this book fills a definite gap in that it supplies normative data for an important group of subjects not covered by previous work. The collection of the data and the presentation of the results are workmanlike and set out so as to be of the maximum usefulness to research workers. On the negative side, it should be noted that the group of children is very homogeneous. Most of them were collected in New Haven, Connecticut, and in nearby towns and cities. These children, therefore, are not even representative of the United States as a whole; it is difficult even to guess what relevance their responses may have to British teenagers. Even worse, the group is highly unrepresentative even of children in that particular locality. Most came from upper middle-class home backgrounds, and their intelligence quotients are well above the average; the mean I.Q. is 116, which is over one standard deviation above the mean. This, of course, is an extremely serious flaw; indeed, it would seem to invalidate completely the use of the data given for the purpose of comparison. The majority of adolescent subjects to whom the Rorschach is administered in a clinical situation tend to come from poor and working-class backgrounds and to have I.Q.s below rather than above average. The differences in their responses from those recorded in this book may therefore be due to cultural or intellectual factors rather than to emotional and psychopathological ones; yet it is almost inevitable that such differences should be interpreted along psychopathological lines. The authors should have tried to hammer this point home rather than gloss over it as they have done.

H. J. EYSENCK.

Tables des Thèses soutenues devant la Faculté de Médecine de Paris en 1958 presents its information as alphabetical lists both of the authors' names and of the subjects dealt with. Veterinary medicine is included. (Librairie Arnette, Paris, 1959; 131 pp.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Anatomia Angiografica del Cane. Tecnica, Metodologia, Atlante Iconografico. By G. C. Canossi, M. Dardari, N. Cortesi, B. Brunelli, and C. Pasquinelli. (Pp. 145; illustrated. L. 7,000.) Turin: Edizioni Minerva Medica. 1960.

Atlas and Manual of Dermatology and Venereology. By Professor Dr. W. Burckhardt. Translated and edited by Stephan Epstein, M.D. (Pp. 276+xiii; illustrated. £5 12s.) London: Baillière, Tindall and Cox, Ltd. 1960.

Safe Handling of Radioactive Isotopes in Medical Practice. By Edith H. Quimby, Sc.D. (Pp. 129+xii; illustrated. 31s. 6d.) New York and London: The Macmillan Company. 1960.

Newer Virus Diseases. Clinical Differentiation of Acute Respiratory Infections. By John M. Adams, M.D., Ph.D. (Pp. 252+xvi; illustrated. 40s.) New York and London: The Macmillan Company. 1960.

Antibiotics and Sulphonamides in Ophthalmology. By Arnold Sorsby and Joseph Ungar. (Pp. 117+ix; illustrated. 12s. 6d.) London, New York, Toronto: Oxford University Press. 1960.

Inflation and Society. By Graham Hutton. (Pp. 161. 15s.) London: George Allen and Unwin, Ltd. 1960.

Marriage: Studies in Emotional Conflict and Growth. Edited by Lily Pincus, with eight contributors. (Pp. 259+vii. 25s.) London: Methuen and Co., Ltd. 1960.

Portrait of Social Work. A Study of Social Services in a Northern Town. By Barbara N. Rodgers and Julia Dixon. (Pp. 266+viii; illustrated. 25s.) London: Oxford University Press for the Nuffield Provincial Hospitals Trust. 1960.

Eternal Eve. The Mysteries of Birth and the Customs that Surround it. By Harvey Graham, M.D. (Pp. 328. 30s.) London: Hutchinson. 1960.

The Purpose and Practice of Medicine. Selections from the Writings of Sir James Spence. With a Memoir by Sir John Charles. (Pp. 308+x; illustrated. 42s.) London, New York, Toronto: Oxford University Press. 1960.

The Eclipse of the Community. An Interpretation of American Studies. By Maurice R. Stein. (Pp. 354+vii. 48s.) Princeton, N.J.: Princeton University Press. London: Oxford University Press. 1960.

A Minority. A Report on the Life of the Male Homosexual in Great Britain. By Gordon Westwood. (Pp. 216+xii. 30s.) London: Longmans. 1960.

The Human Apocrine Sweat Gland in Health and Disease. By Harry J. Hurley, M.D., D.Sc.(Med.), and Walter B. Shelley, M.D., Ph.D. (Pp. 138+x; illustrated. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Transparency of the Cornea. A Symposium Organized by C.I.O.M.S. Edited by Sir Stewart Duke-Elder and E. S. Perkins. (Pp. 268+xii; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1960.

Stress and Psychiatric Disorder. The Proceedings of the Second Oxford Conference of the Mental Health Research Fund. Edited by J. M. Tanner, M.D., D.Sc. (Pp. 151; illustrated. 21s.) Oxford: Blackwell Scientific Publications. 1960.

Stroke. A Diary of Recovery. By Douglas Ritchie. (Pp. 174. 12s. 6d.) London: Faber and Faber. 1960.

Crash Injuries. The Integrated Medical Aspects of Automobile Injuries and Deaths. By Jacob Kulowski, M.D., F.A.C.S., F.I.C.S. (Pp. 1,080+xlii; illustrated. £13.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Myocardosis: Pathogenesis, Clinical Aspects and Therapy with Recent Investigations Concerning the Principles of Metabolic Electrocardiography. By Ferdinand Wuhrmann, M.D. With the collaboration of Serge Niggli, M.D. Translated by Harvey Adelson, M.D. (Pp. 218+xi; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Dynamics of Psychiatric Drug Therapy. Edited by G. J. Sarwer-Foner, M.D. (Pp. 624+xxviii; illustrated. £6 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

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CARDIAC ARREST FROM POTASSIUM GIVEN IN BLOOD TRANSFUSIONS

In the past decade the frequency of cardiac arrest in hospital has increased. H. H. LeVeen and his colleagues[1 2] have studied the possible causes at the Veterans Administration Hospital and the State University of New York Medical Centre in New York City. Of 157 cases of cardiac arrest 50, or about one-third, could be attributed solely to massive blood transfusion.[2] In an additional group of 18, transfusion had contributed to the cardiac arrest. The authors point out that, on storage of blood, potassium leaves the red cells and in the course of 15 days the level of extracellular potassium of stored blood rises from 5 to 25 mEq/l. From the length of storage of the transfused blood and the amount administered they calculated that the 50 patients in whom massive transfusion was the sole cause of cardiac arrest had received on the average 77.7 mEq/l. of potassium.

There are other factors which increase the serum potassium in haemorrhage and shock. In experimental animals a fall in the blood volume increases the susceptibility to cardiac arrest induced by the intravenous injection of potassium salts.[3] This is thought to be due to the release of adrenaline. Anoxia or a rise in carbon-dioxide tension[4] also causes outpouring of adrenaline. This in turn causes glycogenolysis in the liver and release of glucose into the blood. As glucose is released, potassium is simultaneously liberated. This is the reverse of the hypopotassaemia induced during insulin therapy for diabetic coma, when glucose is deposited in the liver and with it potassium.

Liberation of potassium from the liver and the simultaneous intravenous injection of stored blood selectively raise the concentration of potassium in the venous blood returning to the heart. This may not be reflected in samples of peripheral blood which are obtained from the antecubital vein, so that the true state of affairs may not be detected. When cardiac arrest was induced in dogs by the injection of potassium during hypotension and haemorrhagic shock[1] the potassium level in the heart blood was almost three times higher than that obtained from a leg vein. The role of potassium as a causative agent of cardiac arrest may also fail to be detected in the operating theatre, when hyperpotassaemic stored blood is transfused rapidly. The potassium injected into the patient as well as that released from the liver reaches the heart first. The arterial blood then leaves the heart and equilibrates with the extracellular fluid before it reaches the venous side of the circulation, from which blood samples may be obtained. It has been shown[5] that equilibration of radioactive sodium and potassium with extravascular fluid spaces occurs at once. The central, in contrast to the peripheral, blood does not have this opportunity to lose its potassium; a disparity arises therefore between potassium levels in cardiac and peripheral blood, a difference that has also been noted in experiments on subjects in haemorrhagic shock.[6] It has been shown that anoxia of the liver can cause a release of potassium sufficient to induce heart block in the experimental animal even after adrenalectomy.[7] Though potassium is released from all tissues during anoxia, it is so most abundantly from the liver. This potassium, added to that introduced by a rapid transfusion of stored blood, may thus lead to cardiac arrest without evidence of high potassium levels in the peripheral blood.

Methods of reducing the concentration of plasma potassium of stored blood were investigated. Packets of sodium-saturated cationic exchange resins were found to be effective in keeping the plasma potassium levels from rising above 5 mEq/l. even after three weeks of storage. The resin was contained in a small plastic bag which was permeable to alkaline metal ions. Presumably there must be considerable care in using blood treated in this way. Ion-exchange resin acts immediately, and unless the blood bottles have been stored for some time one would expect them to contain no extracellular potassium. A massive transfusion of treated blood which has not been stored for some weeks might therefore cause significant hypopotassaemia. If bottles charged with ion-exchange resin are not available, the authors consider that fresh blood is imperative for all patients in whom massive transfusion appears likely to be needed. In carrying out exchange transfusion of the newborn

[1] LeVeen, H. H., Schatman, B., and Falk, G., *Surg. Gynec. Obstet.*, 1959, **109**, 502.
[2] —— Pasternack, H. S., Lustrin, I., Shapiro, R. B., Becker, E., and Helft, A. E., *J. Amer. med. Ass.*, 1960, **173**, 770.
[3] Rosenthal, S. M., and Millican, R. C., *Pharmacol. Rev.*, 1954, **6**, 489.
[4] Fenn, W. O., and Asano, T., *Amer. J. Physiol.*, 1956, **185**, 567.
[5] Burch, G., Reaser, P., and Cronvich, J., *J. Lab. clin. Med.*, 1947, **32**, 1169.
[6] Zwemer, R. L., and Scudder, J., *Surgery*, 1938, **4**, 510.
[7] Stewart, J. D., Potter, W. H., Hubbard, R. S., and Andersen, M. N., *Ann. Surg.*, 1953, **138**, 593.
[8] MacRae, D. J., and Riley, F., *J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 826.

D. J. MacRae and F. Riley have recommended removing about 100 ml. of the supernatant serum-citrate.[8] While citrate transfusion alone does not induce cardiac arrest, it can increase the toxic effect of potassium by temporarily altering the potassium-calcium ratio. Usually the calcium levels are quickly restored by mobilization of calcium from the bones. However, when citrated blood is being rapidly transfused during haemorrhagic shock, the rate of injection of citrate may exceed the rate of mobilization of endogenous calcium. For this reason LeVeen and his colleagues[2] advise the additional injection of calcium salts. Presumably these would have to be administered into a different vein. Furthermore, digitalis antagonizes the toxic actions of potassium both before and after operation; and, if a cardiac stimulant is required, compounds such as isoprenaline should be given rather than adrenaline.

ANTIBIOTIC COMBINATIONS

The merits of using antibiotics in pairs instead of singly have been a subject of controversy for some years and remain so. One of the advantages claimed for certain combinations is that of synergic action on bacteria, and from time to time some new combination is said to have this type of effect.

Such claims recently made on behalf of a combination of novobiocin and tetracycline had led H. A. Hirsch and M. Finland[1] to examine the action of this pair of antibiotics by an *in-vivo–in-vitro* method which Finland and his colleagues have been using for some years in this kind of study. Single doses of each antibiotic and of mixtures in two proportions, the total dose being kept constant, are administered to normal subjects, and blood samples are taken at intervals for determination of antibacterial activity. In the present study these tests were done with four different bacteria—a streptococcus and a staphylococcus normally sensitive to both antibiotics, a staphylococcus resistant to tetracycline only, and one resistant to novobiocin only. The capacity of the serum to inhibit the growth of these organisms after administering the two antibiotics together was in almost every test exactly what was to be expected from the sum of their individual effects in the doses given, with no suggestion of synergism. The single exception to this was an apparent example of the opposite effect, that of antagonism, though its mechanism was not elucidated. When tested against the tetracycline-resistant staphylococcus, the serum of a subject who had received 250 mg. of novobiocin only was significantly more inhibitory than that of a subject who had been given 250 mg. of novobiocin together with 500 mg. of tetracycline.

This paper is one of a series in which Finland and his colleagues have examined the action of combinations by this method. The first to be studied was penicillin and erythromycin[2]; there followed penicillin and tetracycline,[3] and next a more elaborate study of combinations of various antibiotics with tetracycline.[4] This incidentally compared the activities of three members of this group—erythromycin, oleandomycin, and spiramycin—to the advantage of the first-named, and concluded that, although no combination of any of these with tetracycline was synergic, tetracycline and erythromycin together were more active than tetracycline and oleandomycin, a combination for which far-reaching claims have been made. Further studies were on novobiocin plus penicillin,[5] and penicillin plus chloramphenicol.[6] In none of these studies was any trace of synergism revealed of the kind which is said to have been shown by simple *in vitro* tests; the combined action was always what would be expected from the simple summation of individual effects.

Admirably appropriate as this method of test is, it reflects only bacteriostatic action. The effect of combinations can be examined by two other methods, *in vitro* tests of bactericidal action and animal experiment. Bactericidal action, as distinct from merely bacteriostatic, is all-important in the treatment of bacterial endocarditis and of meningitis. The most consistently synergic combination known, that of penicillin and streptomycin, can be shown *in vitro* to be completely bactericidal for organisms which are not killed by either component alone. Unfortunately the measurement of bactericidal action is a laborious and time-consuming process, and at least when carried out by some methods with multiple strains of the same organism can produce a variety of results, suggesting that species behaviour is far from constant.[7 8] It is certainly wise in any critical case to verify the action of any combination which it is proposed to use in a test with the patient's own organism. The method of animal experiment,

[1] Hirsch, H. A., and Finland, M., *New Engl. J. Med.*, 1960, **262**, 209.
[2] Jones, W. F., and Finland, M., ibid., 1956, **255**, 1019.
[3] —— —— ibid., 1957, **256**, 869.
[4] —— —— ibid., 1957, **257**, 536.
[5] —— —— ibid., 1957, **257**, 1268.
[6] Finland, M., Pryles, C. V., and Jones, W. F., ibid., 1958, **258**, 817.
[7] Elek, S. D., Hilson, G. R. F., and Jewell, P., *Brit. med. J.*, 1953, **2**, 1298.
[8] Jawetz, E., Gunnison, J. B., Coleman, V. R., and Kempe, H. C., *Amer. J. clin. Path.*, 1955, **25**, 1016.
[9] Speck, R. S., Jawetz, E., and Gunnison, J. B., *Arch. intern. Med.*, 1951, **88**, 168.
[10] Jawetz, E., and Speck, R. S., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **74**, 93.
[11] Lepper, M. H., and Dowling, H. F., *Arch. intern. Med.*, 1951, **88**, 489.
[12] Petersdorf, R. G., Rose, M. C., Minchew, H. B., Keene, W. R., and Bennett, I. L., ibid., 1960, **105**, 398.
[13] Barber, M., Dutton, A. A. C., Beard, M. A., Elmes, P. C., and Williams, R., *Brit. med. J.*, 1960, **1**, 11.

appropriately applied on a significant scale, is perhaps the best guide to therapeutic effect, and it is by this means that the clearest evidence has been obtained, not of synergism but of antagonism. Two of the combinations examined by Finland and his colleagues and found to be indifferent have been clearly shown by E. Jawetz to behave antagonistically at critical dose levels in mice infected with streptococci. These are penicillin and a tetracycline[9] and penicillin and chloramphenicol.[10] The mechanism of this effect is clear: it is interference by a bacteriostatic antibiotic with the bactericidal action of another. It is customary to deride such findings as without parallel in the clinical field, but a clear parallel to them has been described,[11] and, though the higher concentrations produced by large doses probably obliterate the antagonistic effect, such combinations may be better avoided. R. G. Petersdorf and his colleagues[12] propose that severe infections by staphylococci of not too high a degree of penicillin resistance should be treated with large doses of penicillin together with chloramphenicol or erythromycin. The action of these combinations, the former in particular, on such organisms seems to deserve study by every possible laboratory method in order to justify their choice for so difficult a purpose.

Synergism is one of the rarer virtues which a combination may possess. Among other advantages claimed perhaps with more general truth is the discouragement of acquired bacterial resistance. The large-scale clinical experiment at Hammersmith Hospital designed to ascertain how true this is in practice was recently described in this journal.[13] The results hitherto are at least encouraging. The view is gaining ground, as the result of this and other studies, that antibiotics to which resistance can develop rapidly, such as erythromycin and novobiocin, should not be given alone, at least for staphylococcal infections in hospitals. On the other hand there are fortunately many conditions in which a single antibiotic can still be relied on. It would be a blow to rational therapeutics and an economic misfortune if it were ever concluded that combinations are advisable always and for every purpose.

MEDICAL RESEARCH IN THE COLONIES

Since 1945, when the Colonial Medical Research Committee was formed, events have moved rapidly both politically and in medical research. For the expansion of research in the British Colonial territories, and indeed the tropics generally, the Committee, under the able guidance of its chairman, Sir Harold Himsworth, must take much credit. When they began their task of advising the Secretary of State for the Colonies on the promotion of medical research, only two universities existed in the Colonies, and in tropical Africa and the Caribbean there were no centres of higher education. There were very few bases in Africa and the Caribbean from which to conduct anything more than *ad hoc* research. Now there are four institutes for medical research in British territories in East Africa and three units in West Africa, together with many centres both within and without the new teaching hospitals in these territories where research is proceeding with support from the Committee.

It was early realized that no single territory could hope to provide in the foreseeable future sufficient resources for medical research to cover more than a fraction of its problems, many of which were common to a large region; much too was clearly to be gained from tackling problems in unison. To deal with this situation the East and West African Councils for Medical Research and a West Indian Advisory Committee for Medical Research in the British Caribbean Territories were established in close relationship with the Colonial Medical Research Committee.

Why, might it be asked, is this arrangement no longer suitable for current needs? The answer is that the funds spent on medical research by the Secretary of State for the Colonies on the advice of the Colonial Medical Research Committee were allocated from those made available by the Colonial Development Welfare Act and could be used only in Colonies to which that Act applies. A colony which becomes independent is no longer eligible for such funds, and though it may have resources enough to replace what it formerly received in this way there is an understandable reluctance among medical research workers to commit themselves to a career where the future is as uncertain as present events make it. It has caused some established workers to leave the Overseas Research Service and has hampered recruitment. The solution accepted by Her Majesty's Government to meet these difficulties is that the work of the existing Colonial Medical Research Committee will be taken over by the Medical Research Council. Under it there will be a Tropical Medicine Board to advise

"(*a*) the Secretary of State for the Colonies through the Medical Research Council on all medical research in or for the Colonies financed from Colonial Development and Welfare Funds;

"(*b*) the Medical Research Council on all medical research in or for the Independent Commonwealth financed from the United Kingdom Exchequer;

"(c) the Medical Research Council on all medical research in or for tropical or subtropical countries financed from their own budget."

The operations of the Medical Research Council are not territorially limited, and for that reason these proposals should provide security of tenure of appointment for those already in the Overseas Research Service of the British Government who are serving in territories soon to be granted independence. They should also provide an attractive career structure for new recruits to medical research overseas. The Medical Research Council proposes to offer to young workers interested in medical problems overseas initial appointments for five years, the first three of which will be spent abroad with the possibility of renewal at the end of this period. If, however, the worker finds tropical work not to his liking he will spend the remainder of the first appointment in a home department allied to his interests. Where research of value is hampered by inability of a newly independent territory to find funds hitherto provided by the Colonial Development and Welfare Act, it should also prove possible for the Medical Research Council with its non-territorially restricted budget to ensure continuity. The proposals will command wide support both at home and overseas, and those concerned with their formulation are to be congratulated on their foresight.

INFECTED COCONUT

An outbreak of typhoid fever and salmonella infection occurring in Australia in 1953 was traced to desiccated coconut contaminated with various organisms of the salmonella group.[1] Numerous strains of salmonella were isolated from the coconut, among them *Salmonella senftenberg*, *S. orion*, and *S. potsdam*, which were the organisms most frequently isolated from infected cases and symptomless excretors. It was only after some time that *S. typhi* was isolated from one sample of the incriminated brand of coconut. This strain was of the same phage type as those isolated from patients in the epidemic who were suffering from typhoid fever. It is perhaps worth remarking that *S. typhi* of this phage type, E.1, was at that time endemic in Australia. All the coconut found to be contaminated had been imported from Papua. Samples of Sinhalese coconut which were cultured during the investigations were free from salmonellae, though they were found to contain a number of coli-aerogenes and paracolon strains. N. Kovacs[2] isolated *S. senftenberg* from 30 and *S. nyborg* from 7 samples of Papuan coconut which he examined during the outbreak, and subsequently isolated salmonellae in 9 out of 35 samples of Sinhalese coconut. One of these samples contained *S. paratyphi-B*; 2 contained a new serotype, *S. perth*; and 5 contained *S. butantan*; only one sample was contaminated with more than one strain, and this contained *S. edinburgh* and *S. perth*.

Between July, 1959, and March, 1960, 851 samples of desiccated coconut imported into Great Britain from Ceylon were tested by members of the Public Health Laboratory Service,[3] and 76 samples were found to contain salmonellae. *S. paratyphi-B*, *S. senftenberg*, and *S. bareilly* were the commonest types isolated. The proportion of samples found to be contaminated varied according to the grade of the material examined. All samples of chippings and flakes which were examined were negative. The highest proportion of contaminated samples was from coconut flour, which was milled in Britain from fine coconut. The authors suggest that the higher proportion of positive samples in flour was probably due to the greater mixing which the material received during processing, leading to a more even distribution of organisms. They could find no evidence that further contamination occurred during milling, though they do not seem to have substantiated this experimentally. There was little difference in the proportion of contaminated samples from bakehouses, docks, or from consignments packed in cases or in paper sacks. The authors concluded from this that it was unlikely that the coconut was contamined after packing in Ceylon. Total bacterial counts at 37° C. were all less than 50,000 per gramme. *Escherichia coli* and "non-faecal" types of coliform bacilli were found in some samples.

There are many opportunities for contamination with organisms of the salmonella group at all stages of manufacture of desiccated coconut. Without going into details of the manufacturing process, it is enough to say that the material is exposed to faecal contamination from humans; animals, including rodents and birds; and from organic and farmyard manures. There is some evidence that the nuts themselves may be permeable to micro-organisms.

It has been shown experimentally that salmonellae grow well on moist coconut flesh in warmth. Although coconut meal is desiccated for about 25 minutes at a temperature of 180°–210° F. (82–99° C.) it has been shown that *E. coli* survived the drying process when the desiccation temperature was 180° F. (82° C.) or more for 40 minutes,[1] and, while the process of desiccation must reduce the number of organisms, it is clear that desiccation alone is insufficient to sterilize the material effectively. Various methods of treating coconut are being tried, including heating to 130° F. (54° C.) for 9 or 10 days; heating to a high temperature for a short time; steam-heating and the use of boiling water; disinfection with ethylene oxide gas; and gamma irradiation.

The numbers of salmonellae present in coconut are so low that infection is likely to occur only when contaminated coconut is in contact with foods which would encourage the multiplication of the organisms under warm, moist conditions, or when large amounts of raw coconut are eaten. When coconut is incorporated in cooked confections it may contaminate other

[1] Wilson, M. M., and Mackenzie, E. F., *J. appl. Bact.*, 1955, **18**, 510.
[2] Kovacs, N., *Med. J. Aust.*, 1959, **1**, 557.
[3] Galbraith, N. S., Hobbs, B. C., Smith, M. E., and Tomlinson, A. J. H., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1960, **19**, 99.

foodstuffs in the kitchen or bakery either directly or by means of utensils or on the hands of food-handlers.

At present port health authorities in Britain sample 5% of imported batches, and if positive results are obtained a further 10% are tested. If positives are found at the second sampling, the contaminated batches are condemned. But, as is the case with so many other imported foodstuffs which are subjected to bacteriological control, the organisms are so unevenly distributed throughout the material that their presence may be missed in samples which are of necessity quantitatively small in relation to the amount in the container being sampled. Production of a bacteriologically safe coconut must depend on improvement in the hygienic conditions in the plantations and factories in the country of origin, and in the tracing and elimination of the sources of contamination, all of which may be a slow process. Alternatively, a suitable disinfecting or sterilizing procedure must be developed which would be applicable on a large scale to the finished product without damaging it or impairing the qualities which make it desirable as an ingredient of puddings, cakes, and confectionery.

AMPHETAMINE OVERDOSAGE IN AN ATHLETE

The increase in body temperature after exercise is entirely physiological and, in general, is no cause for alarm. But sometimes if body cooling is obstructed by clothing, or climatic conditions are unexpectedly severe, heat exhaustion may be induced by exercise, or even heat stroke may develop with a fatal outcome. Football, boxing, and cross-country running have all seen casualties of this type. Now J. Bernheim and J. N. Cox[1] report upon such a case in bicycle racing. Towards the end of a gruelling 119-mile (191 km.) race, which included 7,475 ft. (2,300 m.) of ups and downs, one of the tail, an experienced 25-year-old amateur, was seen to be in difficulties: he collapsed and was immediately taken to hospital. On admission his rectal temperature was 109.4° F. (43° C.), his pulse-rate 140, and his blood-pressure 90/51 mm. Hg. Despite vigorous treatment, including ice packs, he died about five hours later. The body temperature at death is not reported, so the success of the cooling measures cannot be assessed. The immediate cause of death was cardiovascular collapse. At post-mortem examination little abnormal was found except for a hypertrophied heart, minor renal and suprarenal changes, and numerous subseral and submucosal haemorrhages in the viscera, and petechial haemorrhages in the brain.

The picture in this case resembled that described by N. Malamud, W. Haymaker, and R. P. Custer[2] in their report on heat stroke in the U.S. Army, and but for two things one might have accepted this as another example of a man's temperature going too high and reaching the point at which sweating fails.[3] First there are the climatic conditions; although described as "stifling," these were not unduly severe—the temperature was 78.8° F. (25.9° C.) and the relative humidity 56%—especially as cyclists provide their own air movement. No description is given of how this patient was clothed, but no one else in the race is reported to have suffered from the heat. The second discordant note is that the patient's skin on admission was not hot and dry, as is always the case in heat stroke, but of "normal humidity." There was in fact another possible cause of death, amphetamine poisoning. During the race this man had taken 105 mg. of amphetamine, partly in coffee and partly as tablets. Less than 1 mg. was recovered unabsorbed from his stomach.

The authors point out that, although 105 mg. is well below the usually acepted lethal dose of amphetamine, deaths have been recorded after such doses, and the post-mortem findings were as compatible with an overdose of this drug as with heat stroke. They conclude that death resulted from the combination of severe exercise, heat, and amphetamine overdosage. Were it not for the extraordinarily high rectal temperature reported this man's death might have been attributed almost entirely to amphetamine in spite of the size of the dose: certainly the circulatory collapse was probably as much due to the drug as to the heat. Concern about the use of amphetamine by athletes[4] has recently been expressed in the U.S.A. As Professor J. H. Gaddum[5] has written, it induces "a mood of cheerful confidence," which, as in the case of the racing cyclist, may "lead to trouble."

IMMUNOLOGICAL REACTIONS IN SILICOSIS

The capacity of silica to produce collagenous fibrosis in the tissues of man and of many other animal species is still a perplexing problem. The forms of silica capable of doing this are varieties of silicon dioxide often called free silica. In human pathology quartz is the form which is of greatest importance. Other forms of free silica are tridymite, cristobalite, and vitreous silica, which differ from one another slightly in their atomic patterns[1] but they all are chemically 100% silicon dioxide. These four different forms of free silica have considerably different fibrogenic activity. For more than 30 years it had been thought that silicosis was due to the silica going into solution in the tissues, and that the differences in fibrogenicity were related to differences in solubility. This is not so, since the four forms of free silica have equal solubilities, and another explanation must be sought to account for their different fibrogenic capacities.

It is evident that the surface structure of silica particles is important because alteration of it by coating with iron or with aluminium can depress the fibrogenicity. On the other hand, if the outer and more soluble layer of the particles is removed by etching, then the fibrogenicity of the remaining portion of the

[1] Bernheim, J., and Cox, J. N., *Schweiz. med. Wschr.*, 1960, **90**, 322.
[2] Malamud, N., Haymaker, W., and Custer, R. P., *Milit. Surg.*, 1946, **99**, 397.
[3] Ladell, W. S. S., *Trans. roy. Soc. trop. Med. Hyg.*, 1957, **51**, 189.
[4] See annotation, *Brit. med. J.*, 1959, **2**, 1464.
[5] Gaddum, J. H., *Pharmacology*, 1959, Oxford University Press, London, p. 222.

particles is increased although the solubility is reduced. In order to produce its pathogenic effects it seems that quartz must first be taken up by macrophages, and there is clear evidence, as for instance from the work of J. Marks and D. M. James,[2] that quartz depresses the metabolism of these cells and many of the injured cells die. P. F. Holt[3] believes that within the cytoplasm of the phagocytes a collagen precursor is formed which concentrates, polymerizes, and reacts with mono-silicic acid as it is freed from the quartz surface, with the result that pro-collagen is changed into collagen. This is a modified solubility theory.

Other workers, however, have been attracted to a completely different view of silicosis, and regard it as an immunological process. This was first suggested by I. Webster[4] (1954). A good summary of the present position is given by E. C. Vigliani and B. Pernis,[5] and was discussed at the meeting of the Association of Clinical Pathologists last April.[6] Pernis and L. Pecchiai[7] showed that silicotic nodules contain 60% globulins including β- and γ-globulins. These occur as amorphous material in silicotic nodules. Electron microscopy shows collagen fibres embedded in the amorphous substance, the structure thus differing from simple scar tissue. H. Antweiler and E. Hirsch[8] found that quartz coated with homologous serum albumin causes antibodies to form when it is injected into laboratory animals. These antibodies can be detected by agglutination tests. Injected quartz acts as an adjuvant to the formation of antibodies in unrelated immunological reactions—for example, the resistance to typhi-murium infection is increased in mice previously injected with tridymite.[9] The relationship of an unrelated immunological reaction to silicosis was studied by D. E. B. Powell and J. Gough,[10] who showed that the immunization of rabbits with horse serum resulted in subsequent silicotic lesions being larger and more clearly demarcated and more collagenous. The production of anti-egg-albumin in rabbits previously injected with tridymite was five to six times higher than in control rabbits.[11] These observations are pertinent to the observation of A. Caplan[12] that in miners with rheumatic disease the lung lesions are radiologically different from those in miners without arthritic joints. Gough and his colleagues[13] identified a corresponding difference in the pathology of the lesions, showing that pneumoconiosis renders the lung vulnerable to the nodular rheumatoid process. This may be an adjuvant immunological effect. We are left with the question whether silicosis is a specific immunological process or whether the silica merely acts as an adjuvant in other antigen–antibody reactions, and an obvious question is whether the special liability of the silicotic man to develop tuberculosis is in some way concerned with alteration in immunology or in sensitivity to that disease.

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OPHTHALMIC HOSPITAL OF THE ORDER OF ST. JOHN

The new ophthalmic hospital which the Order of St. John has built in Jerusalem is now complete, and a photograph of the building appears in this issue (p. 614). Containing seventy beds and a large out-patient department and incorporating a research institute and training school, the hospital is the most up to date and important ophthalmic centre in the Middle East. It will be opened on October 11 by King Hussein of Jordan in the presence of the Duke of Gloucester, Grand Prior of the Order.

The hospital has a long and eventful history, going back to A.D. 600, when the first hospital was founded to care for the Christian pilgrims to the Holy Sepulchre. When the Holy Land was lost, the Order of St. John moved the hospital first to Cyprus, then to Rhodes, and finally to Malta. After 700 years, in 1882, the Order once again established a hospital in Jerusalem, this time for eye diseases. During the second world war the hospital did invaluable work for the Services and the civilian population, but no sooner had some necessary rebuilding been undertaken than fighting broke out between the Arabs and Israelis, and once again, in 1948, the hospital had to be abandoned. Since then the work has been continued in temporary premises.

The completion of the new building owes much to Sir Stewart Duke-Elder, F.R.S., the Hospitaller of the Order. Five years ago, after exploring the possibilities of co-ordinating ophthalmic work throughout the Middle East, he selected a site, and with the help of governments and industrialists plans were quickly put in hand for the building of the new research institute and the hospital. The former was completed in 1956 and is staffed by a team of workers under the auspices of the Medical Research Council. The two corner-stones of the main building were laid eighteen months ago—one by the Chancellor of the Order, Lieutenant-General Sir Henry Pownall, and one by the Hospitaller, Sir Stewart Duke-Elder—and now the project is complete. The cost so far has been £325,000, and the hospital will need continuing financial support in the future. The importance of its work can hardly be exaggerated, for now that the trachoma virus has been isolated there are hopes that this disease, which is particularly devastating in the Middle East, will be brought under control. The new hospital and research institute in Jerusalem will be one of the spearheads in the final attack against this disease.

Drug Treatment of Disease

PREPARATIONS OTHER THAN IRON FOR THE TREATMENT OF ANAEMIA

BY

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The days when megaloblastic and refractory anaemias were treated with liver, whole or proteolysed, with yeast or yeast-concentrates such as "marmite," and with crude or refined liver extracts for parenteral injection are past. These medicaments owed what success they achieved to their content of factors such as cyanocobalamin and folic acid, and since the active principles are now cheaply available they may be directly prescribed with a consequent gain in specificity and in therapeutic efficacy. In this article only those compounds which have proved clinically effective in one or other variety of anaemia are discussed, and for the more controversial of these some references to original articles and reviews are given. Many other substances, ranging from riboflavin and pantothenic acid to copper, manganese, and other trace elements have been shown to be necessary for normal erythropoiesis in laboratory animals, but deficiencies of these substances severe enough to produce anaemia do not occur in man, and they have not therefore been included. I have also excluded further reference to humoral "erythropoietins" and to batyl alcohol, since, despite their experimental interest, they have not yet established a place in clinical therapeutics.

Vitamin B_{12} (Cyanocobalamin)

This compound was isolated from animal liver in 1948 and identified as the essential anti-pernicious-anaemia factor. Since that time it has become readily available as a product of controlled fermentation by *Streptomyces griseus* and has firmly replaced liver extracts in the treatment of pernicious anaemia, being cheaper, more effective, more concentrated, and much less liable to induce allergic reactions. For initial treatment cyanocobalamin should be given subcutaneously or intramuscularly in a dose of 250 μg. twice weekly for three weeks, the dosage then being reduced to 250 μg. weekly until the haemoglobin has reached a normal level. Maintenance requirements vary in individual patients, but 250 μg. monthly is usually ample for uncomplicated cases, while a similar dose at weekly or fortnightly intervals should be given if there are residual symptoms of subacute combined degeneration of the cord.

Alternatives to parenteral vitamin B_{12} for the treatment of pernicious anaemia have been proposed. They include cyanocobalamin snuff, mixtures of the vitamin with intrinsic factor, peptides, or sorbitol, and mucosal extracts containing intrinsic factor activity. While these various preparations have sometimes been effective and possess the obvious advantage of avoiding the need for injections, none of them can be recommended for routine use at present. They all appear to exhibit a certain irregularity in action and a tendency to become decreasingly effective after a time. The risk of relapse is too serious to be neglected, especially since relapse may be heralded by the rapid development of neurological features rather than by gradual fall in the haemoglobin level.

In megaloblastic anaemias other than pernicious anaemia, when deficiency of cyanocobalamin has been shown to exist by measurement of serum levels or by radioactive uptake studies, parenteral cyanocobalamin again provides the only reliable replacement therapy.

Folic Acid (Pteroylglutamic Acid)

Folic acid, like vitamin B_{12}, is an essential haematinic whose absence or deficiency leads to the development of megaloblastic erythropoiesis, with macrocytic anaemia. The two substances are associated, together with ascorbic acid, in the metabolism of purines and pyrimidines in nucleoprotein synthesis. There is evidence that deficiency of one substance may sometimes be made good, partially and for a restricted period, by an excess of the other. Thus, for example, pernicious anaemia in relapse has been found to respond haematologically with a brisk reticulocytosis and satisfactory rise in haemoglobin when folic acid has been given. The neurological features of pernicious anaemia are not improved, however, and subacute combined degeneration of the cord may occur, sometimes with explosive onset, during the course of treatment. Moreover, folic acid is ineffective for maintenance therapy; even when initial haematological response has been good the haemoglobin level begins to fall again after a variable period of weeks or months. For these reasons, and especially because of the grave risk of serious neurological disorder, folic acid is strictly contraindicated in the treatment of pernicious anaemia. The prohibition applies also to the use of proprietary mixtures containing folic acid for inadequately diagnosed anaemias.

Deficiency of folic acid may arise from many causes, ranging from coeliac disease and idiopathic steatorrhoea to pregnancy and the administration of anticonvulsant drugs. Unfortunately many of the conditions leading to deficiency of folic acid may also cause deficiency of cyanocobalamin, and it may be difficult to determine which deficiency predominates. Discussion of these diagnostic problems is beyond the scope of the present article, but when doubt about the cause of a megaloblastic anaemia exists it seems most reasonable to start treatment with cyanocobalamin injections, and, only if response does not occur or is suboptimal, to replace or supplement these with folic acid (10–20 mg. daily) and ascorbic acid.

Ascorbic Acid

Scurvy is an uncommon disease among civilized populations to-day, and though anaemia may be

prominent among the features of severe scurvy there has been much difference of opinion on whether the anaemia is directly due to lack of ascorbic acid or is secondary to haemorrhage or dietary deficiency of B vitamins. Animal experiments have given rather equivocal answers, and indeed scorbutic states induced in the laboratory have often not been accompanied by anaemia. During the past 10 years, however, a complex relationship has been found to exist between ascorbic acid, the pteroylglutamate complex, and cyanocobalamin which helps to explain the confusing experimental results. It appears likely that all these substances are essential for erythropoiesis, but that partial deficiencies of one may be compensated for by increased utilization of others. Combined deficiencies of moderate degree may readily produce anaemia in laboratory animals, but deficiency of ascorbic acid alone is unlikely to do so unless a severe degree of depletion is achieved and maintained for some weeks. Perhaps the chief function of ascorbic acid in erythropoiesis is as a hydrogen donor in the conversion of folic acid to the active folinic acid (Nichol and Welch, 1950).

As for the clinical importance of ascorbic acid in erythropoiesis in man, the study of Bronte-Stewart (1953) may be taken to establish firmly that anaemia frequently occurs in severe adult scurvy, that it responds specifically to ascorbic acid, and that it has no important element of iron deficiency. The high doses of ascorbic acid, up to 1,000 mg. intravenously each day, given in severe scurvy lead to rapid improvement in the anaemia. Thus ascorbic acid must be regarded as an essential haematinic. Whether less severe deficiencies of ascorbic acid play a part in the genesis of anaemias secondary to intestinal malabsorption in man is less certain; probably ascorbic acid is important in some cases in facilitating the therapeutic action of folic acid and cyanocobalamin (Boscott and Cooke, 1954)

Pyridoxine

In experimental animals diets deficient in pyridoxine have long been known to induce an anaemia characterized by hypochromia and microcytosis but with a high serum iron. A similar anaemia in man, responsive to pyridoxine, was first recognized by Harris and his colleagues (1956), and since that time several more examples of the condition have been reported. Recent case reports with reviews of the literature and discussions of pathogenetic mechanisms include those of Verloop and Rademaker (1960), and Erslev and his associates (1960). Pyridoxine plays an essential part, after phosphorylation, in the earliest stages of haem synthesis, and impaired formation of haem might be expected to result from dietary deficiency of pyridoxine, from inadequate absorption, from faulty intermediary metabolism, or from excessive demand. Whether an individual patient has indeed pyridoxine-deficiency anaemia and which mechanism is at fault is not easy to establish by currently available diagnostic methods, but fortunately a therapeutic trial of pyridoxine, given orally or by subcutaneous injection, is easily carried out, and reticulocytosis with rise in haemoglobin level rapidly ensues in responsive patients. Although the condition is rare, treatment is so effective that pyridoxine should be given a trial in every case of non-thalassaemic hypochromic microcytic anaemia with high serum iron. Appropriate initial dosage of pyridoxine is 50–100 mg. subcutaneously for 4–7 days, followed by oral maintenance treatment of 25 mg. daily or less according to the haemoglobin response.

Cobalt

Although a syndrome characterized by anaemia, anorexia, and wasting is known to occur in ruminants in Australia and Denmark as a result of cobalt deficiency, there is no convincing evidence that dietary deficiency of cobalt ever occurs in man. Nevertheless, cobalt has been used, sometimes successfully, in the treatment of refractory anaemias of various kinds, including anaemias of chronic infection and chronic renal disease, and primary red-cell aplasias (Gardner, 1953; Coles, 1955; Seaman and Koler, 1953). The occasional success of this treatment is not due to the repair of cobalt deficiency but to a stimulation of erythropoiesis, which cobalt has long been known to produce. The mechanism of this action, earlier thought to involve inhibition of oxygen-transporting enzymes and consequent anoxia of the marrow, is now believed to be an indirect one. Goldwasser and his colleagues (1958) have shown that injection of cobalt in experimental animals leads to an increase in circulating plasma erythropoietin, probably as a result of anoxia in the kidneys rather than in the bone-marrow.

The use of cobalt for anaemia is not devoid of hazards. Oral doses of 20–100 mg. of cobaltous chloride daily seem to be necessary, and such large doses may produce nausea, vomiting, and severe tinnitus, while there is a slight risk of inducing goitre and hypothyroidism. There is as yet no reliable method of forecasting whether cobalt is likely to be effective in a given case of refractory anaemia, and unfortunately a therapeutic trial needs to be continued for some four weeks before failure to respond can be assumed. Erythropoietin assays may prove helpful in selecting patients for cobalt therapy, since low levels of plasma erythropoietin might be expected to show improvement after administration of cobalt.

Thyroxine

The majority of patients with myxoedema develop a mild anaemia, frequently macrocytic, which slowly responds to administration of thyroxine in doses sufficient to control the myxoedema. Experimental studies have shown that thyroidectomized animals develop a similar anaemia with decreased erythropoietic activity in the bone-marrow. The mildness of the anaemia, the failure of thyroxine to induce polycythaemia in normal animals, and the normal response to hypoxia shown by thyroidectomized animals all suggest that the influence of the thyroid gland on erythropoiesis is not a specific one, but a manifestation of general metabolic stimulation (Van Dyke *et al.*, 1954). Clinically, severe anaemia in myxoedema is unlikely to be due to thyroid deficiency alone, but to a combination with iron deficiency or even, uncommonly, with pernicious anaemia. In such cases, treatment with iron or cyanocobalamin needs to be supplemented with thyroxine if an adequate response is to be achieved.

Testosterone

The red-cell count and haemoglobin concentration is generally higher in men than in women, and this difference is thought to be due to contrary actions of

testosterone and oestrogens on erythropoiesis, the former providing a mild stimulus and the latter mild inhibition. Mild anaemia may follow orchidectomy both in man and in experimental animals, and this responds to testosterone, but the anaemia is never severe and it is hard to believe that testosterone normally exerts more than a slight and probably non-specific action on erythropoiesis. Nevertheless, occasional examples of dramatic response to testosterone have been observed in patients, especially children, with idiopathic aplastic anaemia (Shahidi and Diamond, 1959), and a therapeutic trial in such patients is certainly justified. The hormone is best given intramuscularly as testosterone propionate 5 to 50 mg. daily, though methyl testosterone, 20 to 100 mg. daily, may be dissolved under the tongue when injections are to be avoided.

A.C.T.H. and Adrenocortical Steroids

These compounds have at least two important contributions to make in the treatment of anaemias. The first results from their effectiveness in suppressing antibody formation and in minimizing the deleterious consequences of antigen–antibody union at cell surfaces, and has its chief application in the treatment of auto-immune acquired haemolytic anaemia. Initial doses as high as 100 mg. daily of prednisone may be necessary to control a serious haemolytic state, but satisfactory maintenance can often be achieved with as little as 5 to 10 mg. daily, and treatment can sometimes be discontinued without relapse after a variable period. Occasional patients who are apparently refractory to prednisone or cortisone respond well to A.C.T.H., but generally there is little to choose between A.C.T.H. and the cortical steroids in therapeutic efficiency, and the latter are most often used because they can be taken orally. The second major use of these steroids in anaemia is the treatment of aplastic and pancytopenic states, when their marrow-stimulating properties may expedite the return of marrow function. Unfortunately their use is successful only in a small minority of cases, but a trial should invariably be made.

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"The number of cases referred to the solicitors during the year shows a tendency to increase, but the amount paid in damages, at £2,384, is less than the amount paid out for some years. The law charges, however, at £5,037, indicate how much it costs to protect the interests of members against claims which cannot be justified." (*57th Annual Report, 1959*, Medical and Dental Defence Union of Scotland Limited.)

MEDICAL ELECTRONICS

DOCTORS AND ENGINEERS IN CONFERENCE

Some 180 papers, lectures, and contributions were presented at the Third International Conference on Medical Electronics, held in London from July 21 to 27. The conference was organized by the Electronics and Communications Section of the Institution of Electrical Engineers in association with the International Federation for Medical Electronics. The chairman at the opening session was Sir WILLIS JACKSON, F.R.S., president of the Institution of Electrical Engineers, and he was supported by Dr. V. K. ZWORYKIN (U.S.A.), president of the International Federation for Medical Electronics, who said that the conference was concerned with the application of the most recent accomplishments in technology, and more particularly electronics, in the medical field.

Among the subjects discussed at the various sessions were instrumentation for medicine and biology, the motor and nervous systems, medical electronics in aviation and space flight, efficiency, reliability, and safety of hospital and medical electronics equipment, instrumentation for physiology and neurophysiology, the circulatory system, electronic aspects of sight, hearing, and locomotion, the respiratory system, ultrasonics and microwave radiation, telemetering, the digestive system, isotopes, radiology, and obstetrics. It is possible to report here only a few out of the large number of papers read at the conference.

Instrumentation in Medical Practice and Research

In his opening address Professor J. MCMICHAEL, F.R.S. (London), said that electronic instrumentation must be welded with medical engineering and with the use of automation in the laboratory. For dealing with the quantitative data which were being accumulated electronic computers would soon come into their own, but he pointed to a real danger of entering on an era of press-button research in the biological field. It was so easy once the apparatus was available to proceed to collect quantitative data, and the application of a few statistics made the whole thing look like a profound contribution to knowledge. "Your instruments extend enormously our powers of observation," he continued, "but this does not necessarily improve our powers of thinking. Our journals are full of ill-digested data rather than research. Often too little effort is made to fit the findings to existing knowledge or to consider how current hypotheses may have to be modified, or even to consider whether the data are really established and acceptable."

The exceptional and the unexpected in research were often the keys to new knowledge. The stimulus to thought arose in the laboratory itself and in the making of observations at first hand by the observer. The joy of research lay in creative activity. While electronics, electronics technicians, electronics engineers, physicists, and physical chemists would be required in increasing numbers and with increasing responsibilities in medical research, the ultimate interpretation of the data would always depend on the biologists, physiologists, and physicians trained to the appreciation of the complex biological variables likely to be at work in the particular experimental circumstances.

Ultrasonics

A session devoted to ultrasonics and microwave radiation evoked particular interest. In a survey of the diagnostic use of ultrasound, Dr. D. H. HOWRY, of the United States, explained that ultrasound was composed of mechanical waves which were generated by the instruments in the form

of short pulses. Those mechanical waves were focused into a narrow beam and were directed into the body through a liquid coupling medium. As the pulse penetrated the tissues of the body, small sound echoes were reflected by tissue surfaces of different densities. The echoes were then received, amplified, and presented as bright spots on a television-type cathode-ray tube. By mechanically scanning the sound beam across the body, multiple bright spots, resulting from the echoes, were formed which coalesced to produce a cross-sectional picture on the cathode-ray tube. A photograph of the screen thus showed a cross-section picture similar to an *x*-ray tomogram. With these instruments it was possible to see the majority of the soft-tissue structures in the neck and extremities, such as the thyroid, larynx, muscles, fat layers, tendons, and blood vessels. The sound waves were of low power and produced no harmful effects of either an immediate or accumulative nature.

Professor I. DONALD (Glasgow) said that during the last year work on the diagnostic applications of pulsed-ultrasonic-ranging techniques in obstetrics and gynaecology had been greatly extended, and some notable observations had been made which promised to be clinically useful. For example, a fibromyoma of the uterus, which was normally not transonic at 2½ megacycles per second, would yield back-wall echoes if it was particularly vascular, and even more so if it had undergone cystic degeneration. By scanning the same tumour at a lower frequency (1½ megacycles) the distal outline was revealed even in the absence of those changes.

Professor Donald said that free fluid within the abdominal cavity displaced the bowel in a characteristic fashion on transverse sectional scanning, but if there were associated masses of ovarian cancer the picture became more complex and bizarre. The coexistence of an ovarian cyst and gravid uterus was easily revealed because of the different echo characteristics of both. With careful scanning twins could be revealed, and it was possible to detect foetal echoes before the twelfth week of pregnancy—considerably in advance of radiology. Notable success had been achieved in identifying the condition of hydatidiform mole, which gave multiple punctate reflections on the cathode-ray screen, in contrast to the comparatively sharp outlines revealed by a foetus *in utero*. Even cases of gross obesity could be usefully scanned in order to determine the presence or otherwise of intra-abdominal tumours which could not be palpated through the massive abdominal wall.

Circulatory System

In another session devoted to the circulatory system, Professor V. V. PARIN from the Soviet Union gave a short lecture on the development of ballistocardiographic techniques in the U.S.S.R. He said that the general conclusion was that ballistocardiography gave valuable information about the contractile function of the myocardium. Ballistocardiography was also important for diagnostic purposes—for instance, in the detection of early manifestations of coronary insufficiency—and could be regarded as a useful clinical tool in the examination of the cardiovascular system.

In the Soviet Union ballistocardiography had been used successfully to investigate the action on the heart of a series of new drugs, to determine the efficiency of physical therapy in spa treatment, for observation on athletes, and finally for mass examination of large groups of the population with the object of early detection of cardiac abnormalities.

In the same session the problems of analysing heart sounds and murmurs were described by Japanese workers Drs. S. YOSHIMURA, S. OBATA, J. SUGAI, Y. SATO, and T. OKAMURA. A study was made of the intensity of vibration of the thoracic wall resulting from the heart beat in order to establish a basis for standardization of phonocardiographs and calibration of the heart sounds and murmurs. Heart sounds and murmurs heard in various heart diseases were analysed, and it was felt that the results would contribute to the solution of some of the problems of modern phonocardiography.

Respiratory System

In a session devoted to the respiratory system, Dr. J. B. WEST (London) gave details of a novel type of bronchial flowmeter which enabled measurements to be made in the segmental bronchi. The flowmeter was introduced through a bronchoscope and sited by direct vision. Measurements of value in the clinical assessment of lung disease and of physiological interest had been made.

Obstetrics

The problem of monitoring continuously the foetal heart rate during labour and delivery was discussed in a paper by Dr. E. H. HON (U.S.A.), who said that the successful clinical use of the equipment in over 80 labours suggested the possibility of simplification and the simultaneous monitoring of several labour rooms from a central desk. In the same session, Professor W. C. W. NIXON (London) gave a lecture entitled "Instrumentation in Obstetric Practice," in which he told those present that he and his co-workers were turning their thoughts to the transillumination of the uterus to detect meconium spectrographically, and to studies of the reactions of the foetus to sound and other external stimuli to ascertain its degree of consciousness and hence of well-being.

Radio Pills

In a session dealing with telemetering of the digestive system Dr. A. M. CONNELL and Dr. E. N. ROWLANDS (London) described the clinical applications of "radio pills" for measuring gastro-intestinal pressures. The main problem was to locate exactly the position of the pill in the gastro-intestinal tract. Fluoroscopy, using an image intensifier, was of help in localizing and in following the progress of the pill. Previous experience of pressure patterns from different sites in the alimentary tract obtained by using calibrated recording tubes had resulted in knowledge of the general appearance of recordings from different levels. That knowledge was very valuable in determining the position of the capsule. In a number of patients the tracings from the pill had been compared with those obtained simultaneously from the same site by means of the more traditional fine polyethylene tubes passed into the intestine: the pressure patterns obtained by the two methods had been virtually identical.

Prospects in Medical Electronics

In a lecture entitled "Prospects in Medical Electronics," Dr. V. K. ZWORYKIN (U.S.A.) said that the most evident trend in electronics was towards miniaturization in both dimensions and power requirements. What did this mean for medicine? First, that electronic probes could be anticipated which could be introduced into organs without interfering substantially with their functioning. Another development which could be anticipated was the insertion of active electronic elements to replace or supplant the action of organs which had become defective. Dr. Zworykin quoted the surgical insertion of heart stimulators as an example. The replacement of such organs as the kidney, heart, or lungs by surgically inserted prosthetic devices with electronic control might seem remote now, but those were goals to which they could properly work.

Electronic equipment in hospital could already perform automatically large numbers of blood and urine analyses, but the time would come when other physical manœuvres connected with the care of patients would be performed automatically.

Finally Dr. V. K. ZWORYKIN suggested that with central stations storing the health records of the entire population in rapid-access electronic memories it would be possible to send out in a continuous stream health questionaries which could be completed and returned by the recipients. The machine, in recording the reply, would compare it with the

data received from the same individuals on previous occasions, and, if the comparison indicated the development of a pathological condition, would send out notices asking the persons in question to seek medical help. The same data-handling systems might be used to construct a giant "Index Medicus" which would help the physician to determine the pathological cause of any set of symptoms presented by a patient and to prescribe a cure for it.

New Appliances

RESUSCITATION APPARATUS

Dr. M. K. SYKES, Department of Anaesthesia, Postgraduate Medical School and Hammersmith Hospital, London, writes: The widespread use of more complicated diagnostic and therapeutic techniques has resulted in a higher incidence of cardiac arrest outside the operating theatre. This complication can be treated effectively only if adequate equipment is immediately available. Unfortunately, such apparatus is often lacking in departments where special procedures are performed. The trolley illustrated in Fig. 1 was designed to satisfy the need for a storage unit which will contain all the equipment required to initiate ventilation and cardiac massage. Since the total cost of the trolley and equipment is approximately £50, a number of such units can be installed to provide full cover for even the most scattered of hospital buildings.

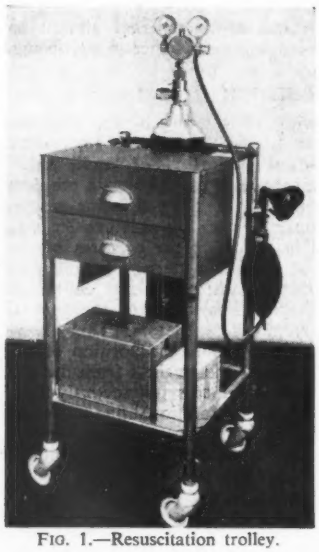

FIG. 1.—Resuscitation trolley.

Two means of ventilating the patient are supplied. The oxygen inflation unit is attached to a combined pressure gauge, reducing-valve, and flowmeter* situated on a 48-cubic-ft. (1.36-cubic-m.) oxygen cylinder. The latter stands within the wheel-base and is locked in position by a hinged bar at the rear. A cylinder key is chained to the stand. A Porton bellows resuscitator (Lucas and Whitcher, 1958) provides a reserve method for inflating the lungs with air.

The top drawer contains two scalpels (dry-heat-sterilized in test-tubes), sterile syringes and needles, and ampoules of 10% calcium chloride (5 ml.), 1/10,000 adrenaline (5 ml.),

FIG. 2.—Perspex emergency pack.

and methylamphetamine (30 mg. in 1.5 ml.). The lower drawer contains pharyngeal airways and apparatus for intubation. The laryngoscope has blades for adults and children, and there is a full range of endotracheal tubes (sizes 00–5 plain, sizes 6–10 cuffed) and connexions. A mouth gag is included; this may be used as an emergency rib-spreader. A list of all the apparatus is attached to the stand for checking purposes.

Apparatus for the further treatment of the situation may be centralized to save expense. Defibrillators and a sterile drum of thoracotomy instruments should be situated within a few minutes' walk of any possible site of cardiac arrest.

Fig. 2 shows another item which may save vital seconds. It consists of a "perspex" tube 35 cm. (14 in.) long with an internal diameter of 19 mm. (¾ in.). It is closed at the ends with rubber bungs which project sufficiently to allow rapid removal. The tube contains a sterile scalpel and ampoules of calcium chloride and adrenaline as detailed above. Such a tube is fixed by Terry clips to the frame of every anaesthetic and analgesic machine in the hospital and ensures that there is no delay in the institution of effective cardiac massage.

I am grateful to Mr. R. G. Smith, instrument curator, and C. Thackray Limited, Leeds, who manufacture the trolley.

*Made by C. V. Bell Limited, Manchester.

REFERENCE

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HARNESS FOR CLIMBING PALM-TREES

Mr. P. H. NEWMAN and Dr. C. WILSON write: Eleven years ago a scheme was started by the Colonial Office to send specialists in medicine and surgery to Colonial territories. At the outset the Nuffield Foundation offered to help the Colonial Office in financing such a project, but after an arranged trial period of six years the funds expired, and it is interesting to note that the individual territorial Governments elected to continue the scheme at their own expense.

Under this scheme one of us (P. H. N.) visited Nigeria, Sierra Leone, and Gambia in the autumn of 1957 for the purpose of studying and reporting on the cause and treatment of accidents and orthopaedic conditions. During the tour many hospitals were visited, and it was estimated that between 10 and 12% of all beds were occupied by accident cases, which, divided into four main groups, gave these figures: road 46%, industrial 27.5%, domestic 18.5%, and sport 8%. It was surprising that more than a quarter of all accidents were industrial in territories depending so little on mechanized industry. The commonest and gravest form of accident at work was falling from a palm-tree. It was not possible to get exact figures, but it became evident that the number of cases admitted to hospital gave a very low estimate of the total, as fatalities were common and most of these accidents occurred in inaccessible places, leaving the injured to be accommodated in their own village.

The harvesting of the fruit from palm-trees is a most important matter in the economy of West Africa, and accidents due to falling from a tree often have the most serious results, immediate death being by no means rare. Broken neck or back is a frequent outcome often complicated by paraplegia, a most distressing state for the patient and presenting a major transport and nursing problem. The more fortunate victims reach hospital, but the others are left to endure agonies of distress in their own homes till death relieves them. Once in hospital the patient remains there, often to occupy a bed for a very long time.

Most tree-climbing in West Africa is done with the aid of an encircling vine cut from the bush. The girdle consists of one or more strands bound together with string or natural binding material in an apparently carefree manner. The ends of the girdle have to be separated each time, and once the tree is encircled the ends are bound together or knotted. Accidents happen for three main reasons: (1) breaking or giving way of the girdle; (2) severing the girdle with the cutlass which the native uses for cutting the fruit; and (3) a slip due to wet weather, foolhardiness, or fright from an animal, snake, or insect up the tree.

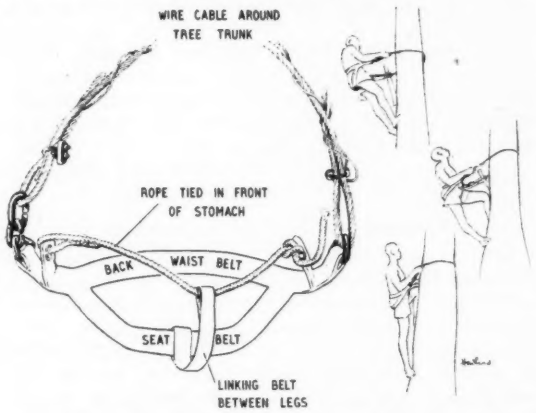
Though large plantations are now cultivating short types of tree which do not necessitate climbing by the harvester, the small farmers, who are greatly in the majority, still live by their tall palms, and will continue to do so for many years.

This apparent lack of interest on the part of climbers in their own personal security, the frequency of accidents, the suffering, and the wastage of valuable hospital beds were factors which obviously merited attention, and for that reason the problem of accidents resulting from tree-climbing was reported to the Ministry of Health of the Nigerian Federal Government in Lagos with a suggestion that a research project should be started into the safety of palm-tree climbing and the design of an efficient harness for this purpose.

The Ministry of Health responded promptly, and invited one of us (C. W.) as Chief Medical Officer of the Cameroons Development Corporation to make inquiries and to be responsible for further investigations.

The Cameroons Development Corporation readily gave its permission for the work, and what has resulted is largely due to the help which many of its staff gave most willingly—in fact, the prototype illustrated here is largely the work of Mr. Walkling, of the Shipping Division, who devised the harness as it now is and was instrumental in having it made. The main essentials of the harness are that it should be easily constructed, be made from materials readily obtainable in most parts of the tropics, and be acceptable to those who had to use it.

To satisfy the first two essentials, canvas is easily available in most places, and was therefore considered suitable for the body section of the apparatus, and wire cable, of which some is to be found almost anywhere, for the tree section. The difficulty was finding something suitable for the junction of these, as hooks with spring catches are not easily procurable and are apt to become unsafe if the spring rusts, as is more than likely in humid countries. Filed chain-links were thought to be most suitable, as used for the signal hoists of the Royal Navy. The harness consists essentially of two parts, the body belt and a loop to encompass the tree.



The idea of attaching the tree loop to a simple belt was investigated only to be discarded, as it did not place the fulcrum in quite the right place for the action required for the climb. Instead of that, trial was given to a pair of bulky canvas shorts with the tree loop attached where the top of the pockets would normally be inset. This, however, was somewhat uncomfortable, and eventually the body belt, which consisted of two canvas straps, was evolved. The straps were made of canvas folded on itself and sewn into position, joining each other at an angle of about 30 degrees, one being slightly shorter than the other. The shorter has attached to it a short, narrower strap with a loop at its distal end for use as a crutch strap.

The ends of the longer strap were fixed to a piece of reinforcing iron bent in a triangle and with one part of the chain link. The ends of the shorter strap were pierced to take a small piece of rope, which was spliced to one end, and, after passing through the loop of the crutch strap, was tied to the other end across the lower abdomen for adjusting the harness into place. We have used brass cringles for this piercing, but sewn buttonholes are just as good. The pierced strap is inside the other one, or the fixation rope would interfere with movements of the cable loop for going round the tree. The tree loop is made of wire cable with each end bent back on itself and fixed with a bulldog clip. Splicing was tried, but this allowed no adjustment for the individual or the girth of the tree.

One or two minor matters required attention. In the first place, the wire cable, which was 1-in. (2.5-cm.) cable, was too flexible. This was overcome by loosely winding around it some galvanized-iron wire. This gave it all the rigidity necessary. The other main trouble was that in the prototype, to save links, one end of the wire was attached direct to the harness triangle and a split link at one end only. This means that any user who has to walk any distance between climbs has to remove the whole harness or walk holding the wire loop in a clumsy position. If, however, split links are fixed to both ends of the loop it becomes detachable from the harness and the wearer becomes much more mobile. The cost of this apparatus should not be expensive to the individual, as every material used is reasonably available and little skill is required in making it up. On plantations with engineering facilities it should be very simple to produce, and the little expenditure involved will rapidly repay itself in fewer accidents and much less time spent in hospital or money paid in compensation. In practice it has been found that the apparatus is acceptable to practically all the harvesters, though with some it is not what "they were used to use" and therefore not acceptable at present.

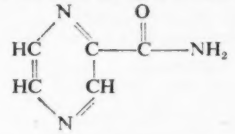
Our thanks are due to the Palms Division of the Cameroon Development Corporation for all the assistance and co-operation they gave, and to Miss E. Hewland for the illustration.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Pyrazinamide (Merck Sharpe and Dohme).

Chemistry.—This is pyrazinoic acid amide, an analogue of nicotinamide, and has the following structural formula:



Pharmacology.—This antituberculous drug acts only on human tubercle bacilli, best at a pH of 5–5.5 *in vitro*. In mice, but less so in guinea-pigs, pyrazinamide alone has a moderate antituberculous effect, but this is greatly enhanced by adding isoniazid.

Therapy.—In man, resistance to pyrazinamide alone develops in four to six weeks, so that, except as a temporary addition for operative cover, this drug should always be given in combination. Pyrazinamide in a dose of 40–50 mg. per kg. body weight (1–1.5 g. b.d.) together with 100–150 mg. twice daily of isoniazid forms a most potent combination. The sputum may become negative by the fourth month in up to 93% of fresh cases,[1] often with radiological improvement. This regime is comparable in effect to P.A.S. with isoniazid.[2] Combination with daily streptomycin[3] or *para*-aminosalicylic acid[4] may produce equal results.

It follows that, when a patient's organisms are resistant to two of the three standard drugs, an effective combination with the remaining drug and pyrazinamide is possible, and probably is the most powerful therapy now available to the patient. Surgical treatment may be indicated later, since it is uncertain whether any of these combinations can ensure arrest.

Resistance to streptomycin, P.A.S., and isoniazid presents a much greater difficulty. Tetracycline does not prevent the emergence of pyrazinamide resistance,[5] but viomycin may be more effective.[6] Some reports have claimed moderate success when cycloserine 500 mg. daily is combined,[7] but experience in Great Britain has been rather disappointing. The most effective combination of pyrazinamide may be that with 1314TH (*alpha*-ethylisonicotinic acid thioamide), the latter in doses of up to 1 g. daily, but this is being assessed in current trials. The clinician may feel that a combination of three or more of the above drugs may be more potent, though toxicity is increased. In some patients none of these combinations will arrest advanced disease; surgery at the optimal moment is often essential.

Primary pyrazinamide resistance occurs occasionally, so that pretreatment sensitivity tests should be done. When even low degrees of resistance to a second drug exist, resistance to pyrazinamide will emerge.[8]

Toxic Effects.—Hepato-cellular damage, often resulting in severe and at times fatal jaundice, may occur in up to 12% of patients and usually during the first few months of treatment.[2] Routine tests of liver function should be done at least fortnightly; the most sensitive is the level in the serum of glutamic oxalacetic transaminase. Allergic, gastro-intestinal, skin, and gouty manifestations are rare. Because of this definite risk of hepatitis, pyrazinamide should never be given as a primary treatment except when resistance to at least two of the standard antituberculous drugs is present.

Contraindications.—Permanent liver damage is a contra-indication. Renal disease may cause retention and abnormally high blood levels of the drug.

N.H.S. Basic Price.—0.5-g. tabs., 100 for £5.

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7 Toguri, E., and Atwell, R. J., *Amer. Rev. Tuberc.*, 1958, **78**, 927.
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ORDER OF ST. JOHN OF JERUSALEM

Those recently appointed to, or promoted in, the Most Venerable Order of the Hospital of St. John of Jerusalem include the following members of the medical profession:

As Knights: Air Commodore T. K. Lyle, C.B.E., and Drs. J. N. B. Crawford, M.B.E., E.D., and S. G. H. Gasson. *As Commanders (Brothers):* Surgeon Rear-Admirals W. P. E. McIntyre, Q.H.P., and G. Phillips, Q.H.S., Surgeon Rear-Admiral T. B. McLean, R.C.N., Surgeon Commander J. A. Watson, R.N., retired, Brigadier J. G. Morgan, C.B.E., T.D., Major T. MacF. Wilks, O.B.E., T.D., Messrs. J. S. Grant and R. H. Percival, and Drs. E. P. Coyne, H. L. Garson, O.B.E., M.C., A. R. McPherson, G. M. S. Smith, E. I. Puddy, V.R.D., S. C. H. Lane, O.B.E., and J. T. Daly. *As Officers (Brothers):* Surgeon Captain E. B. Bradbury, R.N., Major-General W. D. Hughes, C.B.E., Q. H. P., Brigadier E. H. Ainslie. R.C.A.M.C., Colonel J. C. Reed, C.B.E., Colonel E. E. Tieman, O.B.E., R.C.A.M.C., Group Captain G. D. Caldbick, R.C.A.F., Mr. D. R. Jennings, and Drs. M. Theodoulou, L. E. Claremont, J. A. Dryden, A. Ll. Potter, M. T. I. Jones, R. E. Crockatt, W. Adams, J. S. Moffat, E. W. Q. Bannerman, W. R. H. Pooler, T. M. F. Fitzgerald, W. J. Boyd, O.B.E., E.D., D. J. H. Meredith, N. R. Jefferson, C. A. Taylor, J. G. Campbell, N. F. Murphy, F. R. C. Johnstone, H. E. Wilson, and B. S. Tulloch. *As Officer (Sister):* Dr. Hilda M. Shand. *As Serving Brothers:* Surgeon Commander A. W. W. Robinson, R.N., Surgeon Lieutenant-Commander C. A. West, R.C.N., Lieutenant-Colonel G. McCracken, and Drs. A. Rose, V. H. Barker, J. Carey-Hughes, J. B. A. Reynolds, S. J. Evans, E. ap Cynon, J. W. R. Battram, M.C., H. Herbert, J. E. E. Hughes, W. P. Philipps, O.B.E., J. M. Davidson, K. H. Walter, W. W. Cashmore, H. D. Eddy, M.C., G. Lancaster, J. S. Hunter, J. K. Corrigan, A. F. D. Carrie, C. Sharp, B. W. Wood, O. P. Edmonds, S. W. Wolfe, C. D. Drew, R. V. Bannister, C. H. G. Bowes, F. M. Bourne, N. S. Knapp, and C. L. MacLellan. *As Associate Serving Brother:* Dr. L. M. Gerlis. *As Serving Sister:* Dr. Joan M. MacKinnon.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Gangrene from Thiopentone

SIR,—Once again it has been shown conclusively by Professor J. H. Burn (August 6, p. 414) that while thiopentone may cause gangrene of the hand if accidentally injected into the brachial artery, there is no record of hexobarbitone ever having caused similar damage. Patients who have been induced successively with thiopentone and hexobarbitone report that there is no difference in the ease and speed of induction. As to duration of action, in my own experience a single injection of hexobarbitone given to a patient undergoing surgery under regional block has produced unconsciousness lasting for three hours twenty minutes. It has been shown that the incidence of laryngeal spasm under hexobarbitone is one-quarter of that under thiopentone, while an overdose of hexobarbitone does not cause respiratory depression to the same extent as thiopentone.

It is true that hexobarbitone never produces muscular relaxation and occasionally gives rise to involuntary twitching, but with the almost universal use of a muscle relaxant drug following a barbiturate induction these defects are no longer a contraindication to its use. When teaching students it is a great advantage to allow them to induce anaesthesia with hexobarbitone, as any errors of technique will not give rise to disastrous consequences.

Yet, despite the known dangers of thiopentone, anaesthetists all over the country continue to use it, presumably from habit. It is to be hoped that Professor Burn's article may remind them of the continued risk they are running.—I am, etc.,

London, W.1. MASSEY DAWKINS.

Treatment of Skeletal Tuberculosis

SIR,—I would be one of the first to congratulate Professor John Crofton on his lucid and authoritative articles on the treatment of tuberculosis with antibiotics (July 30, p. 370, and August 6, p. 449). It may, however, be permissible to add a postscript on the treatment of skeletal tuberculosis with antibiotics, because the pathological conditions which are present in skeletal tuberculosis differ from those which are present in pulmonary tuberculosis, and it is very doubtful whether it would be possible to obtain the same excellent results in skeletal tuberculosis by prolonged antibiotic therapy alone that Professor Crofton obtains in pulmonary tuberculosis.

Sanchis-Olmos[1] summarizes these differences by saying that the elasticity of the lungs favours the spread of exudative pulmonary disease, and similarly massive exudative disease in the lungs can resolve completely. The opposite occurs in bones, because the tissue is rigid and necrosis occurs early and rapidly and may be extensive; nor can the necrotic and sequestrated areas recover without surgical intervention. Operation may be needed early to prevent bone necrosis, or later to clear the bone or joint if necrosis has occurred. Excellent and rapid results are obtained in the treatment of tuberculous bones by the combination of constitutional, antibiotic, and operative treatment, and, although antibiotic treat-

ment may be more important than either of the others, it is not of itself capable of producing results of the same excellence as those obtained by the use of the three methods in combination. Indeed, many joints would be lost unnecessarily if reliance were placed only on antibiotic treatment. With the combined therapy, antibiotic treatment is not necessarily required for so long a period as eighteen months.

A large number of patients treated by constitutional treatment, antibiotics, and operation have now been followed up, and, although the majority of these patients received only three months' antibiotic treatment, the number of relapses have been few. My present practice is to give, in combination with the other forms of treatment, antibiotics for at least six months, or for longer if there is any special indication, and so far this has been found to be adequate.—I am, etc.,

Black Notley Hospital, Braintree, Essex. M. C. WILKINSON.

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Congenital Heart Block

SIR,—Mr. J. Eyton-Jones's interesting report of two cases of congenital heart block (July 23, p. 275) may perhaps perpetuate two myths. The first is that septal defects (atrial or ventricular) can cause heart block. The second is that congenital heart block carries a bad prognosis.

Congenital heart block results from failure of the conducting tissues (atrial muscle, A.V. node and bundle) to achieve continuity. Congenital septal defects are only exceptionally associated with heart block and are never causal. This is logical when the developmental anatomy of the conducting system is considered.[1,2] Mr. Eyton-Jones refers to a case of congenital heart block "due to an interauricular septal defect" described by McNie and Johnstone.[3] These authors did not in fact attribute the block to the septal defect.

A few children with congenital heart block have associated heart malformations and die young. The remainder usually have functional murmurs which may lead to the erroneous diagnosis of septal defects. Congenital heart block without associated cardiac malformations carries an excellent prognosis.—I am, etc.,

Department of Child Health, University of Liverpool. R. W. SMITHELLS.

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Streptomycin and Labyrinthine Atax'a

SIR,—In the past fortnight I have seen four severe cases of labyrinthine ataxia, due to streptomycin. In only one of these could it entirely be certain that this particular drug was indicated—a case of pulmonary tuberculosis. In the other three patients, all elderly women, a surgical condition was treated with this drug, and the unsteadiness of legs was noticed for the first time when the patient got out of bed. In all three, the period of treatment was short, and in one case lasted only five days. Disability was sufficient to prevent the patients from going outdoors and it had lasted several months, and in one woman for more than a year.

If sufficient thought had been given, it seems likely that a less toxic drug could have been substituted for the streptomycin. In spite of the paper by Cawthorne and Ranger[1] and the occasional cases where heavy damages have been paid for this complication (Smith *v.* Brighton and Lewes Hospital Management Committee),[2] surgeons still do not appear to be aware of the dangers of administering this drug to elderly dehydrated patients. How many more times must neurologists and otologists issue the warning ?—I am, etc.,

London, W.1. K. W. G. HEATHFIELD.

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Infants and the March of Medical Science

SIR,—It is interesting to observe the march of medical science as reflected in successive editions of the *National Formulary*. This is especially noticeable in the Infants' Section. Two editions ago (in 1955) this section contained three antibacterial mixtures. Now in 1960 one of these has been deleted, leaving us with two—mist. sulphadimid. pro inf. and mist. succinyl . . . etc. (always an awkward one to spell). No mention of anything discovered since about 1938.

If the infant needs any more modern antibacterial agent it has presumably to put up with something from the general section: a nasty injection perhaps. Or it could bite off half a capsule. Or (if its mother is a capable do-it-yourself apothecary) it could swallow a tablet crushed up in something tasty. Otherwise—perish the thought—it might be tempted to enjoy a concoction made by one of those unmentionable proprietary manufacturers.—I am, etc.,

Watford. R. C. TAYLOR.

Nature of Congenital Dysphasias

SIR,—Dr. Macdonald Critchley in the Centennial Oration of the Institute of Neurology (July 2, p. 6) asks: "What is the essential nature of the so-called congenital dysphasias, including developmental dyslexia and congenital auditory imperception ?" His pertinent remarks in answer have prompted this letter.

In attempting to understand the psychological abnormalities in children of about 7 years of age who are unable to speak or comprehend the spoken word, the scheme of intellectual development outlined by Jean Piaget, of Geneva, has been found helpful. Three such cases were recently observed as in-patients at the Montreal Children's Hospital where I was a senior assistant resident in psychiatry. It is hoped that one of these will be published in detail shortly.

This is an 8-year-old boy who has never shown any inclination to speak or respond to speech, although he appears normal emotionally, morally, and physically except for a left-sided E.E.G. epileptic focus. The audiogram and pneumoencephalogram were without abnormality. Several non-verbal intelligence tests were at his age-level or above—e.g., Raven's matrices, Nebraska, Goodenough, Bender. Well-developed spatial concepts were shown to be present using some of Piaget's clinical tests.[2] Since speech failed to appear it is not surprising that logico-mathematical concepts are poorly developed. Those that he has have been revealed by his use of written words, an ability he recently began to show. Symbolism,[3] the representation of one thing by another, is well developed. He plays for long periods and can reproduce situations some time later by drawing them.

This disorder appears to be an inability to use auditory signs. By using the conceptual framework and methods of developmental psychology, it is felt that progress in understanding congenital auditory imperception will be made.—I am, etc.,

Leeds, 17. IAN BERG.

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Collapse after Oral Diuretic

SIR,—May I be allowed to report a case of alarming collapse following the use of "hygroton"?

The patient, an obese lady of 65, consulted me because of oedema of the legs and ankles, exercise dyspnoea, and knee-joint pains. On examination, apart from obesity and ankle-oedema, there were no physical signs except occasional extrasystoles. The B.P. was 160/100. I advised a reducing diet and prescribed hygroton 100 mg. on alternate mornings, with calcium aspirin for her osteoarthritis. On the third day after I had seen the patient she awoke feeling slightly "muzzy." She took her third hygroton tablet at 10.30 a.m., and one hour later she felt dizzy and faint, and I was urgently called in.

On arrival, five minutes after being summoned, the patient was collapsed, cold, clammy, cyanosed but conscious. Pulse was very difficult to feel, heart sounded faint, and B.P. 90/60. She had no chest pain or headache, and because the diagnosis was not clear I merely put the patient to bed, called in a consultant, and watched events. At 12.30 p.m. the patient's colour was good, pulse regular at 84 and of good volume, B.P. 120/80. When the consultant arrived, three hours after the collapse occurred, physical findings were the same as at 12.30 p.m., but B.P. was then 150/100. An E.C.G. was within normal limits. The consultant attributed the collapse to reduction in blood volume and electrolyte disturbance, and informed me that he had seen two similar cases within a few days following chlorothiazide therapy.

My patient, who has recovered, admitted having lost 3 lb. (1.4 kg.) in weight during the three days following the commencement of therapy, and the significant facts are that the patient had not been put on digitalis and had taken only her third hygroton tablet when the collapse occurred. It would seem that in some patients such gross diuresis can follow even small doses of these new diuretics alone, and that severe hypotensive features may result.—I am, etc.,

London, E.9. C. J. G. FRANKLIN.

Medical Study of Radiesthesia

SIR,—In your summary of the judgment in the case of "Radionics and the Black Box" (July 30, p. 398), Mr. Justice Davies is reported to have referred to the "Medical Society for the Study of Radionics." To give the society its correct title, "Radiesthesia" should be substituted for "Radionics."

The word radiesthesia is the modern name for the ancient art of dowsing. This society, whose membership is restricted to registered medical practitioners, is concerned with its application to medical problems.

In radionics specially designed instruments are used which, it is claimed, are of value in the wider field of radiesthesia. It is regrettable that not infrequently provocative claims of results obtained are made by people using such instruments, claims which appear seldom to be supported by carefully controlled experiments.—I am, etc.,

London, S.W.1. MICHAEL MCCREADY.

Child Psychiatry

SIR,—While everybody would agree with the need for a comprehensive training and a wide experience in the associated branches for the consultant child-psychiatrist,[1] and the recommendation for an expansion of the national establishment of senior registrars and consultants in the field,[2] it remains a paradoxical fact that during the past ten or more years relatively few new senior posts were created, although lip service has been paid to the need at all levels of medical and local administration, and suitable young men are not attracted to the career of children's psychiatrist in spite of their ever-increasing interest in the theoretical psychopathological and sociological importance of this specialty. There are many psychiatrists very keen to devote a session or two, or to accept a full-time engagement for a limited period, but few are willing to devote themselves exclusively to child psychiatry. It would therefore seem more important to find out the reasons for this reluctance than to reiterate the numerical need for establishments which neither are likely to exist in the near future nor would ever be filled by suitable candidates. There is hardly any other specialty which requires more super-specialized training, as the family, educational, social, and cultural factors in the life of childhood mentioned in your annotation (July 16, p. 205) are not covered even by the most comprehensive D.P.M. course. The child-psychiatrist must possess also certain personal qualities to understand and guide children or parents, and to be able to co-operate efficiently and without friction with various non-medical experts and interested departments. These cannot be assessed at a single interview, but only after observation during prolonged training. Unless the right type of candidates will be forthcoming the theoretically needed establishment will either never be filled or the specialty, which is already very critically viewed by psychologically minded paediatricians, may be diluted by the appointment of inadequate candidates and fall into undeserved disrepute.

It appears to me that nobody has yet found the solution. Perhaps the professional disadvantages of joint appointments needs further investigation, or the children's psychiatrist needs more reassurance that he is neither disowned by his colleagues in the mental hospital nor rejected by the paediatricians. His status versus the educational psychologist in the child-guidance clinic may need more emphatic protection by the regional hospital board, or he should be assured of more adequate opportunity for treating his patients, with the necessary clinical assistance to shorten his ever increasing waiting-list, without being inundated by clinically unimportant but administratively urgent requests for reports and statements. Perhaps some far-sighted young psychiatrists even feel that if they should tire of contact with children after years of work and with advancing age, the return into the fold of general psychiatric practice would be impossible without losing status. Or should we make, in the interest of the national need, even more sweeping changes, and tap the pool of psychiatrically minded paediatricians, provide them with a comprehensive post-graduate training course in general psychiatry, and allow them to work on equal footing with psychiatrists as "psychiatric paediatricians" in child-guidance clinics? These are not personal problems, because, like any of my colleagues who have matured in the work for which they have felt a vocation, I have solved the questions satisfactorily to

myself, but we should know what it is that prevents new recruits from joining the ranks.

Nothing less than a nation-wide research project by carefully devised questionaries, or preferably skilful interviewers, arranged by a university department, the R.M.P.A., or the B.M.A., involving budding and experienced psychiatrists and paediatricians, perhaps also medical administrators on a local and regional level, could provide the answers and establish how the very urgent and vital problem of providing an adequate number of skilled psychiatrists for the child-guidance clinics of the nation can be filled. This might prove a big and expensive task, but worthy of the Mental Health Year.—I am, etc.,

Leicester. A. K. GRAF.

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Psychiatry in General Practice

SIR,—I fully agree with Dr. L. M. Franklin (August 6, p. 451) when he states that "the flood of mental illness with which the G.P. has to contend presents problems that are hard to solve," but I question the title of his paper, "an appraisal of psychiatry in general practice," and with all humility I would suggest that the paper be called "an appraisal of psychiatry in *his own* practice." If Dr. Franklin limits his psychotherapy to "two or three interviews" with patients for a "personal discussion between patient and doctor," it is hardly surprising that his results are discouraging. In discussing methods of psychotherapy with many other doctors it appears that there are a number of different types of psychotherapy which in the first place may be divided, as surgery is divided, into major and minor branches.[1]

Having considered the results of a psychiatric approach in general practice by a number of other doctors, as well as in my own experience, my findings are very different from Dr. Franklin's, and for the sake of brevity I give the reference to a recent account of them.[2]

Without taking up too much of your space I wish only to say that a reasonably advanced interpretative form of minor psychotherapy is well within the competence of any family doctor who is prepared to undergo a course of suitable training and who has the temperament that will not only allow him to be self-critical but also to be criticized by his colleagues. I attended one of the Tavistock Clinic's seminars, supervised by Dr. Michael Balint, which Dr. Franklin feels are difficult to justify. Having attended this seminar for three and a half years I can say with some conviction that had it not been worth while I would not have continued for so long. Furthermore I can testify to the usefulness of the time spent at the seminar when I know how much more I can help a large number of my patients by using various psychotherapeutic methods than I could ever do using only the more orthodox physical methods of which Dr. Franklin appears to hold such high hopes.

The "single technique" referred to by Dr. Franklin does not exist. Each doctor attending a seminar develops his own techniques, which vary from one patient to another, and I know of no way of learning about this other than by attending a seminar-type of course. That there are many other family doctors who will agree with me is shown by the number of doctors who are attending groups of this sort throughout Britain together with the ever-growing waiting-list for places in the seminars at the Tavistock Clinic.

In other countries too the recognition of the need for a fuller understanding of patients' needs is growing, so that a postgraduate course organized by the Dutch College of General Practitioners and the University Hospital, Leyden, in May, 1960, attracted 400 Dutch general practitioners for a discussion of psychological medicine. Previous courses on more orthodox subjects drew only 80 or so doctors each year. I was one of a group of doctors from Britain who visited Leyden for the week-end course, together with others from America, France, and Germany, and the discussion showed that we were all faced with the same problems. While visiting the U.S.S.R. recently with a medical delegation to study the Health Service I was told by a leading Russian professor of psychiatry that one of his research projects was to examine the role of the personality in the pathogenesis of illness.

Dr. Franklin rightly emphasizes that "diagnosis must form the basic rational treatment," but he begs the question as to what the diagnosis really is. Frequently the diagnosis is not apparent until the patient has been seen for a number of sessions, and in many cases the initial or provisional "diagnostic tags" can only then be properly replaced by the true diagnosis in terms of the patient's emotional state in relationship with his total environment. Only then may he be helped adequately.

It may be that the help needed consists of manipulation of the environment, as, for example, in the provision of new housing or of a new job. Possibly a new wife is the answer, or it may be that the patient is a psychiatric cripple who must "become dependent on the doctor," as Dr. Franklin puts it. This does not seem any more terrible to me than the dependence of the patient with diabetes or pernicious anaemia, although it may certainly be much more difficult to accept. The important point is that the doctor should be aware of what is going on in the situation and consciously try to fulfil each patient's needs in the way required of him, so that he knows what he is doing in each case.

Not only is the psychiatric approach in general practice important for the individual but also for the whole family. I have used "ill-health charts" to show how the unhappiness of one member of a family can lead to illness in other members of the family as well as in himself.[3] By a form of family group-therapy it is possible to treat not only the individual illnesses but also the situation producing them.

Finally, may I disagree with Dr. Franklin's prophecy that "the next big advance in the management of mental illness in general practice is likely to result from the elaboration of new methods of physical treatment"? Time and again I have been disappointed in the effects of the newest and most highly praised tranquillizers when I had hoped for a short cut in the treatment of some of my more difficult patients. It seems to me that in the same way that alcohol does nothing more for one's troubles except irrigate them a little, so drug-therapy in the treatment of patients with psychiatric and psychosomatic illnesses can do no more than the paint applied to the cracks in the wall—simply cover them up for a short time. Health and happiness are indivisible and the doctor cannot escape from this truth.—I am, etc.,

London, N.W.3. PHILIP HOPKINS.

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SIR,—Having read Dr. L. M. Franklin's article (August 6, p. 451), I feel he so misunderstands the position of the G.P. seminars at the Tavistock Clinic that I should like to comment from the standpoint of a G.P. attending such a seminar.

Dr. Franklin implies that he is a non-partisan observer, but it is quite clear that he feels the future of

psychiatry lies in the hands of the biochemists, the only non-physical means of treatment he employs being short term "personal discussion" in young adults with fresh anxiety states, and hypnosis for dysmenorrhoea, migraine, and asthma.

This wish for chemical pie in the sky does not solve what he describes, correctly in my view, the immediate problem of how to help the doctors as they now are to deal with the patients who actually consult them.

He calls on us to have perspective about our patients' chronic illnesses, and states that symptom tolerance is a rewarding exercise. He does not suggest—or perhaps he is using suggestion—how we should acquire this tolerance and teach it to our patients. The Tavistock seminars certainly produce such a tolerance in the majority of doctors attending them. They also help in tackling a rather wider field of disorders than anxiety states in young adults, migraine, dysmenorrhoea, and asthma. It is "irrelevant diagnostic tags" that we are warned against, as they impose too rigid a framework of thought, not diagnosis in the true sense. We are not devoting so much time to a single technique, but to a reappraisal of the whole field of mental disorder, which was given a disproportionately small amount of attention in most of our student curricula.

However, the greatest charge he levels at the seminars is their poor results, and the high loss of doctors prematurely ceasing to attend. The real point is that the Tavistock Clinic does not seek to offer a panacea, and the realization of this is often disillusioning, but seeks to form a partnership of psychiatrists and G.P.s on an equal footing in order to research into the pressing problems of which Dr. Franklin is so clearly aware.

It is in this field, *par excellence*, that we general practitioners can further the science of medicine. Let us not adopt a passive role, whatever our convictions.—I am, etc.,

London, S.W.11. M. J. F. COURTENAY.

SIR,—I have read Dr. L. M. Franklin's article on psychiatry in general practice (August 6, p. 451) with interest, and although he expresses some opinions to which I could not subscribe (notably in his pessimistic paragraph about hysteria), there is only one comment that I wish to make. In the article there is no indication that he ever calls in a psychiatrist in consultation or sends his patients for an opinion to a psychiatric clinic. It would be interesting to know if in fact he does so, and, if so, how often?—I am, etc.,

Beaconsfield. J. B. S. LEWIS.

Vacuum Extractor in Obstetrics

SIR,—I would like to comment on Mr. J. A. Chalmers's statement (July 9, p. 149) ". . . and only when the cervix is three-quarters or more dilated should the ventouse be employed." It has been my experience with the vacuum extractor that the degree of dilatation of the cervix is of little consequence. Having used the instrument in 55 cases in the first stage of labour, I have had equal success when the cervix is two or three fingers dilated as when it is almost completely dilated. Since the use of the vacuum extractor is essentially a means of accelerating normal labour, it is reasonable to assume that any case which is suitable for vaginal delivery can be delivered with the vacuum extractor irrespective of the condition of the cervix. Naturally, however, the degree of dilatation of the cervix will influence the duration of the delivery, and it has been my practice to restrict the use of the instrument in the early first stage of labour to those in whom the cervix is almost completely, or completely, taken up.

I know Malmström is also of this opinion. In 1958[1] he suggested to me a procedure of "induction-delivery." This was to apply immediately, in suitable cases, after surgical induction by artificial rupture of the membranes the smallest cup and begin delivery without any previous labour. I have not heard if he has put this plan into practice, but such a procedure should be feasible in a suitable multipara and might on occasions prove very useful.

Chalmers and Fothergill[2] contend that the vacuum extractor cannot completely replace the forceps. To go a step further, I think that any obstetrician who is reasonably skilled in the use of forceps will find few indications for the vacuum extractor in the second stage of labour. I feel that the chief indication for its use is in cases of prolongation of the first stage of labour due to inefficient uterine action. Thus to limit its application to those cases which have attained three-quarters or greater dilatation of the cervix would be to restrict its usefulness and would only serve to lessen interest in an instrument which has great potentialities.—I am, etc.,

Rotunda Hospital, Dublin. E. W. LILLIE.

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Oral Contraceptives

SIR,—It is satisfactory to read in the report on this subject (July 30, p. 380) that there is no likelihood of the tablets being carcinogenic and that in a patient suffering from cancer they "might have a tendency to arrest it." On the other hand I am a little worried that in one-third of the cases there is a side-effect of "break-through bleeding," which may occur up to four cycles, and the patients are told to ignore this. In a few years' time there may be millions of women taking these tablets and ignoring irregular bleeding. For those of us who are "stumping" the country trying to persuade women to pay more attention to irregular bleeding because of the remote possibility that it may be due to early-stage malignant disease, this side-effect is most discouraging. Everybody realizes the importance of this method of contraception, but it is to be hoped that some change can be made in the composition of the tablets to avoid this very serious side-effect.—I am, etc.,

Cancer Information Association, Oxford. MALCOLM DONALDSON.

SIR,—In the statement under this heading by the Medical Advisory Council of the Family Planning Association (July 30, p. 380) there appears the following (p. 381):

"Ovarian biopsies have been obtained from women who, after using norethynodrel as a contraceptive for some time, have wanted to be sterilized. These women were always sterilized during the last two weeks of a cycle . . ."

This would seem to imply that the only reason for performing these sterilizing operations was to procure permanent immunity from conception at the request of the patient concerned (who may well have been

influenced in her request by her husband) and were therefore unlawful if performed in the United Kingdom.

Although there is no decided case on this point of law, the council of the Medical Protection Society, in conjunction with the councils of the other two defence societies, took the opinion of eminent counsel, both in England and in Scotland, on the legality of human sterilization a few years ago. These opinions were that the only circumstances in which an operation to sterilize a person can be lawfully performed are those in which the operator honestly believes upon reasonable grounds that such an operation is necessary to preserve the life, or to avert serious injury to the physical or mental health, of the patient.

Counsel advised that whatever other steps a doctor may feel he should take to bring himself within the law in such cases, he should never omit (1) to make sure that such danger to life or health as is described above exists; (2) to obtain in all cases where possible a second opinion; (3) to make quite plain to the patient the nature of the results of the operation; and (4) to make sure that the patient's consent in writing is freely and fully given without undue influence by others.

Counsel also advised that if these principles are properly applied both surgeon and patient should be safe from any suggestion of infringement of the criminal or civil law. If, however, the operation is unlawful then it may very well be that both surgeon and patient will have rendered themselves liable to a criminal charge and possibly the patient in certain circumstances to divorce proceedings based on cruelty.—I am, etc.,

ALISTAIR FRENCH,
Secretary,
Medical Protection Society.

London, W.1.

Accidental Arsenical Poisoning

SIR,—In view of the report (July 16, p. 242) of death following the use of "S.V.C." pessaries the following case history may be of interest.

A patient, aged 41, developed a heavy vaginal discharge due to *Trichomonas vaginalis*, which did not respond to "sterisil" (hexetidine) gel or "penotrane" (phenylmercuric methylenebis) pessaries. There was no previous history of drug allergy, and a three months' course of S.V.C. pessaries (twice daily) was begun on February 19, 1960. Ten days later the patient complained of frontal headache, which gradually increased in intensity over the next fortnight. On the morning of March 15 she was found unconscious in bed and was admitted to hospital. On admission she had recovered consciousness but was still drowsy and showed marked mental confusion, but there were no other localizing signs in the central nervous system.

The investigations showed the cerebrospinal fluid to be normal in pressure and content. A blood count and *x*-ray examination of the skull and chest were also normal. The electroencephalogram was abnormal, showing paroxysmal outbursts of 2–3 c/s slow waves of high voltage throughout both hemispheres, but more marked over the frontal regions than elsewhere. For the next five days drowsiness and mental confusion alternated with periods of relative alertness, although at no time was the mental state normal. Five days after admission she had a major convulsion and her general condition deteriorated rapidly. Further E.E.G. recordings had shown a persisting abnormality similar in type to the first record; this, taken in conjunction with the clinical picture, gave support to a diagnosis of "encephalitis" possibly of allergic type.

She was given hydrocortisone 100 mg. intramuscularly and prednisone 10 mg. four-hourly. Within 24 hours there was a rapid improvement in the patient's clinical condition, and in a further 48 hours she was alert and co-operative. Treatment with steroids was gradually reduced, and discontinued after four weeks. The E.E.G. abnormality persisted for a fortnight, but then reverted gradually to normal over a period of three months. She is now quite well.

Encephalomyelitis has been reported following small doses of carbarsone orally in the treatment of amoebic disease.[1] Furthermore, encephalopathy is now a well-recognized complication of treatment with N.A.B., and there is no apparent relationship between the severity of the disease and the dose used.[2 3] Study of the case reports shows that symptoms usually appear within two to three weeks of commencing treatment.

In the case referred to in the *Journal* (July 16) death followed the use of S.V.C. pessaries, and it was considered that death was due to acute arsenical poisoning. The history of the patient described above, where the onset of symptoms occurred within 10 days of starting treatment (a total of 80 gr. of acetarsol being used), gives some grounds for the belief that encephalopathy may complicate treatment with arsenical pessaries.

I wish to thank Dr. E. C. Hutchinson for permission to refer to the hospital notes.

—I am, etc.,

JOAN ACHESON.

Stoke-on-Trent.

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Long Cord

SIR,—I was most interested to read Dr. P. F. R. Lankester's letter (July 23, p. 311) in which he reports an umbilical cord 165 cm. in length. This is one of the longest cords reported in recent literature but is not a record.

In their series of 177 cases, Walker and Pye[1] report the longest cord as 121.9 cm., and in a personal series of 110 cases studied at this hospital the longest cord was 120 cm. However, Gardiner[2] quotes Leray who reported the length of the umbilical cord in 10,457 cases, the longest in this series being 172 cm. In the same article he mentions a case reported by Cazeau, in which the umbilical cord was 300 cm. long; this surely must be the record.—I am, etc.,

PETER STALLABRASS.

Institute of Obstetrics and Gynaecology,
University of London,
London, W.6.

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2 Gardiner, J. P., *Surg. Gynec. Obstet.*, 1922, **34**, 252.

Pitfalls in the Treatment of Tuberculosis

SIR,—The following case reveals yet another hazard associated with the treatment of tuberculosis.

A 6-year-old boy was admitted to hospital with an acute primary pulmonary tubercular complex. He had not been immunized against poliomyelitis (on the grounds that he was asthmatic). He was treated initially by rest in bed. His condition deteriorated. Isoniazid by mouth and streptomycin by injection were added, the injections being given in alternate buttocks. His condition gradually improved, the temperature slowly settled, appetite improved, the E.S.R. began to drop. Six weeks after the start of chemotherapy, when his condition had ceased to cause anxiety, he suddenly

vomited, his pyrexia returned, he developed meningeal signs, and complained of pain in one leg. The C.S.F. showed the typical changes of poliomyelitis. A thorough epidemiological investigation failed to reveal any source of infection. The consequences have been tragic. Now, practically a year later, the child has an extensive residual paralysis of both legs.

The following conclusions appear justified. The infection must have been contracted from a member of the hospital staff or from a visitor, probably a symptomless carrier. The location and extent of the paralysis was governed by the site and frequency of the injections. It may well be that with a wider use of immunization the carrier rate may be increasing ; if so, the risk to the uninoculated must increase. Such tragedies as this may not be rare. I would be grateful for your readers' views on how such tragedies might be avoided. Should streptomycin in the unprotected be withheld and so run the risk of drug resistance ? Is it possible to start treatment with isoniazid by mouth combined with active and/or passive immunization, streptomycin being added later when some degree of protection has been acquired ?—I am, etc.,

The Royal Infirmary, Huddersfield. W. P. SWEETNAM.

Suxamethonium Muscle Pains

SIR,—With reference to Dr. R. J. T. Woodland's letter (July 30, p. 393) that subsequent muscle pain apparently never occurs after suxamethonium used in conjunction with electroplexy, this has been investigated here, and it has been found that the incidence of muscle pains is substantially reduced but is not completely abolished following this procedure.

In the investigations there were 111 patients (all ambulant ; ages ranging from 17 to 70 ; 59 males and 52 females with diagnoses ranging from anxiety states and depression to catatonic and paranoid schizophrenia) who had between them 671 " treatments." On each occasion the patient received 25 to 50 mg. suxamethonium after 200 to 300 mg. of thiopentone (dose depending on body size). Each patient was up and about within one hour. There were only three occasions when patients complained of having muscle pain, while a further one (male) was not sure. On these three occasions one patient (female) complained twice after each of two " treatments " while one other patient (male) complained once but not after subsequent " treatments."

Thus it would appear that electroplexy confers a substantial degree of protection against suxamethonium after pains but does not abolish them.—I am, etc.,

The West Hill Hospital, Dartford, Kent. P. J. TOMLIN.

Doctors' Letters

SIR,—Dr. John Fry in his letter (July 30, p. 384) invites discussion on the subject of doctors' letters. Most of what he says would find general agreement: a few points, though, are controversial.

Surely letters from hospital should not be filed in the patient's medical record envelope. These letters are the property of the recipient, and may sometimes be couched in the most personal terms (e.g., " Dear Tom," or ending with an invitation to dinner, etc.), so that they should be filed separately. Some patients acquire literally dozens of such letters in their name, and they would soon render the record envelope an unmanageable and useless document ; moreover, the N.H.S. has been going only 12 years. A precis of the hospital findings should be written on the medical record card, and, at the expense of a little extra writing, will provide the brief but salient details of that patient's clinical history.

Contrariwise, many hospital letters are the opposite of personal. They seem to be written to a stereotyped pattern ignoring anything that the G.P. has suggested or asked. This may be a matter of hospital record policy. However, there would seem to be a place for a combination of the two types of letter. For instance, on the day an out-patient is seen, or an in-patient is discharged or dies, a brief personal letter could be sent to the G.P. (and this could be extended, as Dr. Fry suggests, to a note on the disposal of the acute surgical emergency which is admitted). It is likely that this type of letter would be of more practical use to the G.P. than the more formal full report. Moreover, it is also likely that it would revive the G.P.'s interest in his case, and at the same time make the patient feel as if he is merely being transferred to the G.P.'s care rather than being turned out of an institution to fend for himself. Care of a patient is a combined effort between those " at the hub " and those " at the periphery," and if those " inside " and those " outside " are doomed seldom to meet, surely the facility of correspondence between them must be important.—I am, etc.,

Chertsey D. G. DAVIDSON.

Abdominal Epilepsy

SIR,—In his review of Dr. John Apley's excellent little book, *The Child with Abdominal Pains* (July 9, p. 120), Professor Wilfrid Gaisford says that the myths of abdominal migraine and epilepsy are therein exploded. This is rather a sweeping statement, and may in fact be merely a reflection of the personal prejudices of the reviewer. On reading the book carefully it is evident that even Dr. Apley admits that sometimes masked epilepsy is a cause of recurrent abdominal pain. The explosion is in fact not atomic but conventional, and not very effective at that.

The main argument against the concept is the old one that it (I quote Apley) implies a serious disorder and may itself provoke unfortunate personal, familial, and social reactions. If we are to stop making diagnoses for such reasons we may as well give up the practice of medicine. Suppose we treated syphilis like that ! Abdominal epilepsy is not exploded: far from it. In this country some opinion is against it, as always against anything new or unorthodox. But in America and on the Continent enlightenment advances.[1-4]

May I quote from Werner Laurie's biography of James Lindley ? " It is a sad reflection on the way the human mind works but it is unhappily true that the courage and boldness of any new proposal can nearly always be gauged by the amount of opposition and ridicule with which it is greeted. And the most distressing thing of all is that the opposition and ridicule nearly always come from people who are well informed and should know better."

It may seem useless to revive the old arguments and academically they are unimportant. But when children are the sufferers it is necessary to take action to prevent further damage being done. I refer once again to Moore.[5] " Most of the patients suffering with this disorder have in the past been hospitalized numerous

times, subjected to scores of examinations and varied forms of therapy without relief, and have had needless laparotomies done. Only too frequently they have been considered as psychoneurotics or malingerers." I hope that the review will not have done much to further the recurrence of such unfortunate happenings.—I am, etc.,

Bath. HUGH WALLIS.

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Achromobacter Anitratus

SIR,—We are grateful to Dr. George X. Trimble (July 2, p. 71) for drawing our attention to the article by Drs. H. Rocha and L. B. Guze, which we had not noticed. The three cases reported are most interesting. We still maintain that the conclusive evidence we found at necropsy, and which has not been described before, makes our report the first which establishes this organism as an undoubted pathogen.—We are, etc.,

A. PINES.
D. L. GARDNER.

Departments of Tuberculosis and Diseases of the Respiratory System and Pathology, University of Edinburgh.

Prothrombin Time Abroad

SIR,—Dr. A. F. Mohun's problem (July 23, p. 308) may be solved comparatively simply. Since as clinical pathologist Dr. Mohun controls the management of anticoagulant therapy, he would be welcome to apply for membership of the European Society of Haematology, whose Seventh Congress was held in London in September, 1959. The list of members of the society contains names of those who are either in a position to undertake control of anticoagulant therapy in their laboratories or can refer patients to their colleagues who are only too willing to help in the control. The society has now over 800 members in almost all European countries. I shall be glad to help Dr. A. F. Mohun to compile the list he requires, but believe simple reference to the list of members of the European Society of Haematology will be sufficient.

Most haematologists will oblige by doing the test asked for, whether it is the Quick one-stage or the thrombotest, and state the results in seconds rather than in per cent. or index. Although I share Dr. Mohun's views about the comparative uselessness of "activity," "index," or "percentage," we cannot, I feel, dictate to those who may help our patients abroad.—I am, etc.,

Department of Pathology, St. Mary's Hospital, London, W.2. E. NEUMARK.

Urinary Test for Imipramine

SIR,—With reference to Dr. J. G. Hegarty's letter "Urinary Test for Imipramine" (June 4, p. 1736) we would like to bring to your attention that we previously published two clinical notes[1 2] on the same subject. Based on the reaction of imipramine and its urinary metabolites with the dichromate ion, yielding a scale of green colour complexes according to concentration present, our test offers the following advantages.

The reagent (consisting of 25 parts 0.2% potassium dichromate solution, 25 parts 30% sulphuric acid, 25 parts 20% perchloric acid, and 25 parts 50% nitric acid) is added to the urine in a single step at the rate of 1 ml. of reagent to 1 ml. of urine, or, in the presence of substantial amounts of phenothiazine drugs, 2 ml. of reagent to 1 ml. of urine, and the resulting colour is read promptly against a colour chart, showing four different levels of intensity from 25 to 250 mg. daily drug intake. The reagent is stable and thus eliminates separate addition of "a small amount" of potassium chromate or dichromate and concentrated hydrochloric or sulphuric acid. The addition of concentrated acids to urine alone frequently yields unspecific darkening and discolorations.

The sensitivity of our reagent is also superior. Whereas relatively high doses of 75 mg. imipramine per day occasionally yield negative tests according to Dr. Hegarty, doses of 25 mg. per day show up distinctly in our test, and frequently as little as 10 mg. per day can be reliably demonstrated and semi-quantitatively evaluated, even in the presence of high doses of phenothiazine drugs. Small daily doses from 10 to 50 mg. yield rapidly fading colours, while higher daily doses produce more stable colour complexes. Thus all readings should be taken promptly. While no false negatives were seen, a few false positives (4 in 300) were encountered in a series of control urines containing all types of drugs. All of the four false positives were obtained from patients on high doses of multiple anti-tubercular medication, especially para-aminosalicylic acid, the pale olive-green colour appearing with some delay.—We are, etc.,

IRENE S. FORREST.
FRED M. FORREST.
AARON S. MASON.

Veterans Administration Hospital, Brockton, Mass.

REFERENCES

1 Forrest, Irene S., and Forrest, F. M., *Amer. J. Psychiat.*, 1960, **116**, 840.
2 —— —— and Mason, A. S., ibid., 1960, **116**, 1021.

Vasodilator Drugs in Peripheral Vascular Disease

SIR,—Dr. J. F. Goodwin (June 11, p. 1800) suggests that vasodilator drugs are of little value in the treatment of peripheral vascular disease. The management of secondary vascular disease as a sequel to neuromuscular failure in a limb is not discussed. In particular the limb with little or no functional muscle due to gross nerve injury or poliomyelitis becomes a cold limb which has repeated thermal trauma in cold weather. Whether these blue ulcerated legs can truly be said to be merely the result of severe chilblains is probably more a semantic than a diagnostic problem. In general the peripheral skin temperature in these limbs is at or very close to ambient temperature. Sympathectomy, although initially effective, is rarely of lasting benefit; within two or three years the limb is again cold and subject to thermal trauma.

The sequence of failure in these limbs on exposure to cold appears to be: (1) Normal skin vasoconstriction on cooling. (2) Absence of metabolically active deep tissue results in greatly diminished total blood flow in the limb. (3) Greater surface heat-loss than that gained from arterial blood entering the limb results in progressive cooling of the limb from the periphery. This cooling includes the main vessels and causes further vasoconstriction. (4) Ultimately blood supply becomes inadequate for normal skin nutrition, particularly if the limb is now warmed, there being an appreciable time lag before circulation is re-established to the artificially warmed area.

Prevention of this type of damage is dependent on maintaining a blood circulation adequate to heat the limb, and this circulation is much in excess of that for metabolic requirements. To this end vasodilators are very suitable. Commonly they do not entirely prevent the limb getting cold, but they do result in rapid re-establishment of circulation with ambient temperature rise, and will allow healing or prevent skin damage in the majority of cases.

Dosage of a suitable drug is difficult to ascertain. Many subjects can be benefited by doses as low as, for example, 12½ mg. of "priscol" b.d. or t.d.s., whereas higher dosage causes distressing side-effects, and the initial dosage should routinely start at a low level. On the other hand, other patients increase to as high as 400 mg. daily without significant toxic or therapeutic effect. Many of these patients will respond to low dosage of an alternative drug.

I would be interested to know of any experiences in this field with very young children. I have used this technique with some misgivings in children aged 3 with apparent success, but assessment of toxic effects can be very difficult, the minimal dose being used which will produce therapeutic results.—I am, etc.,

Department of Health, Poliomyelitis Division, Victoria, Australia. PETER L. COLVILLE.

Carpal-tunnel Syndrome

SIR,—Dr. R. S. Crow (May 28, p. 1611) gives the impression that the main treatment of the carpal tunnel syndrome is still operative decompression. There may be many causes for the increased volume of the structures which pass beneath the retinaculum, but surely the commonest is salt and water retention, and the "standby of treatment" must therefore be chlorothiazide, assisted if necessary by a little prednisone.[1] A somewhat comparable "tunnel" is the auditory canal and labyrinth, and the above regime is not infrequently successful in Ménière's disease as well as in the early case of nerve deafness and tinnitus.

The daily dose of prednisone should not exceed the level that is necessary for physiologic replacement and for the routine control of the constitutional sensitization disorders—i.e., for women and children 5–7½ mg., and for males 7½–10 mg., depending upon age and physique. To those who are still using surgery, splints, and injections, may I suggest an initial trial of the above approach and in the above dosage for the "idiopathic" case?—I am, etc.,

Christchurch, New Zealand. H. R. DONALD.

REFERENCE

[1] Donald, H. R., *N.Z. med. J.*, 1960, **59**, 2.

Contrecoup Fracture of the Sternum

SIR,—Dr. J. Blair Hartley, in his presidential address to the British Institute of Radiology,[1] has reviewed the mechanisms of stress and fracture of the first ribs. One of these mechanisms, acute anteflexion of the spine, appears identical with the reported mechanism of fracture of the sternum.

According to Dr. Blair Hartley various protective mechanisms also operate in this area. It would therefore be interesting to know if the cases reported by Mr. Miles Fox (March 26, p. 935) and Dr. James Simpson (May 14, p. 1505) had protective arthrodial joints in their presumably calcified costal cartilages or not, and if the case detailed by Dr. Lloyd K. Morgan (July 30, p. 392) showed any anomaly of his first rib or early calcification in his costal cartilages.—I am, etc.,

Edinburgh, 4. G. B. YOUNG.

REFERENCE

[1] Hartley, J. B., *Brit. J. Radiol.*, 1959, **32**, 561.

Overseas Career Appointments

SIR,—I have to-day received my *Journal* of July 2, and hasten to support the suggestions made by Dr. R. Morton Mitchell (p. 67). Experience, unfortunately, does not engender optimism. One would have imagined that had H.M. Government seriously wished members of the overseas service to continue serving in the newly independent territories it would, even if unwilling actively to encourage them to do so, not have actively discouraged them from so doing.

In Nigeria new expatriate recruitment is all done on a short-term contract basis. Such recruits have their salaries loaded with an "inducement" allowance. Members of H.M. Overseas Service who have elected to change their terms of service from a "permanent" to a contract basis receive an "abatement" addition. Those overseas service officers who continue to serve in the permanent service receive neither allowance. The effect of this is that their salaries are 20% less than those of their birds-of-passage colleagues. The "abatement," I should emphasize, is paid by H.M. Government. Moreover, the pensions of those who have elected to leave the permanent service under this contractual scheme have been guaranteed by the home Government. This guarantee has not been extended to the other overseas service officers.

H.M. Secretary of State for the Colonies announced the other day that he wished to explore ways to induce his officers to continue to serve in newly and about-to-become-independent territories. Nigeria would seem to be a good avenue in which to turn a few stones while laying the foundations of a new era. I wish I could think it reasonably likely that H.M. Government will show much concern for our careers. If we were Cypriots, with hidden arsenals and strategic importance, I would feel more optimistic. If we were Maltese, with some strategic value, even though unarmed, there might be a ray of hope. But, alas, we are only British doctors—and we haven't even a vote.—I am, etc.,

Ibadan, Nigeria. THOMAS B. RANKINE.

Mental Health Tribunals

SIR,—Surely few doctors will disagree with Dr. F. E. Graham-Bonnalie's amendment to a motion to the A.R.M. in June, that a general practitioner should be included as a member of each mental health tribunal (*Supplement*, June 25, p. 419). Apart from any other consideration, there is no group of individuals more familiar with home conditions in general than general practitioners, and home is the hoped-for destination of the incarcerated patients.

However, the present-day co-operation between the medical staff of mental hospitals and general practitioners will make mental health tribunals only a second line of defence for the unnecessarily retained patient. My experience is that early reports are given promptly on request and I have been encouraged to visit my patients, whether or not I have asked to. The general practitioner can therefore act as a bridge over the deep

gulf between mental hospital and home. He can, as likely as not, reassure those at home that, thanks to advances in psychiatry, there will be no recurrence of the state the patient was in prior to admission. I have found that a visit from their general practitioner, a friend from home, free from the usual prejudices, results in a marked improvement in the patient's morale. I am tempted also to suggest that this can be a deciding factor in the ultimate prognosis.

As Dr. Myrtle M. Hutchins says (July 16, p. 233), psychiatry is keeping pace with scientific advancement in other fields. The rapidity of the pace is such, however, that the definition of psychiatric terms has been unable to keep up. Until it does, psychiatrists will be unable adequately to communicate their knowledge to others, and much of the benefit of the advancement will be lost. —I am, etc.,

Barton-on-Humber, Lincs. S. H. F. HOWARD.

Minister of Health

SIR,—In your article on the new Minister of Health (August 6, p. 460) no mention has been made of Mr. Enoch Powell's lengthy service on the Council of the Chest and Heart Association. A regular attender, he has recently been our honorary treasurer. Our loss will be a severe one, especially to the medical half of the council.

With good wishes for success and perchance some enjoyment in his office, may some of us live to know that he and Sir John Charles are again in the building overlooking Parliament Square, surely the right place for the Minister and his permanent staff.—I am, etc.,

Church Stretton, Shropshire. G. LISSANT COX.

Rod and Serpent

SIR,—Several of your readers have been good enough to write to me on the subject of the Aesculapean rod and serpent as a result of my letter in your issue of May 28 (p. 1654).

The theory of a "Narcissan" snake gazing at its own reflection seems to be more widespread than one had supposed. I have received from Dr. Herrimann, of Bonn, drawings of the badges of the Army medical services of most European countries. France, Belgium, and the Netherlands have the "looking-glass snake," while Great Britain, Germany, and Switzerland show the orthodox staff. In the badge of the apothecaries of Switzerland and the Netherlands, the serpent is coiled around what looks like a champagne glass. It also appears on the badge of the dental services in all countries except Great Britain. The nursing services are not represented.

Great Britain appears to be the only country in which the veterinary surgeons are not included in the medical services, and the Aesculapean symbol appears in different form in the veterinary service of other countries. Our own R.A.V.C. carries a representation of the centaur Chiron, and this is not entirely irrelevant, for, as your readers will recall, it was Chiron who taught Aesculapius the healing art. To have been half a horse must have presented some difficulties in carrying on medical practice, though it doubtless solved many transport problems.

The two intertwined snakes of the Hermes–Mercury caduceus, deprecated by Dr. Hymie Gordon (July 2, p. 72) as being more suited to an association of undertakers, was worn by the Fascist Militia (Blackshirts). It also appears on the badge of our R.A.F. Medical Service.—I am, etc.,

R.A.M.C. Historical Museum, Church Crookham, Hants. R. E. BARNSLEY.

SIR,—With reference to Major-General R. E. Barnsley's letter on this subject (May 28, p. 1654), I think it originated from Hindu medicine.

The Hindu Yogis believe that man possesses every power if only he knows how to acquire and activate it, and that power is known as Kundalini. This Kundalini, crooked in form, is described as being coiled like a serpent, and is sleeping above the kanda or stem. Sir John Woodroffe, the author of *Serpent Power*, has described Kundalini as the Grand Potential. And this, on being roused, ascends. In her ascent she has to traverse six chakras or plexuses along the stem or spinal cord. By the establishment of that control of the Kundalini, or serpent power, one is said to gain supernatural power by which we can perform miracles.

The originator of healing human ailments probably sought refuge in this serpent power, and took it as a symbol—a stem, or spinal cord, and the Kundalini, or the snake, with its six crooked turns in the process of ascent.—I am, etc.,

State Hospital, Mudon, Burma M. R. DAS GUPTA.

**This correspondence is now closed.—ED., *B.M.J.*

Fools and Wise Men

SIR,—A further word concerning the origin of the expression on fools versus wise men (July 2, p. 6, and July 30, p. 393). I am obliged to Dr. M. N. Pai for his explanation, as I had first heard the expression in Australia in 1945, but with no reference to the author. In Birmingham last year a daily calendar with a tear-off date sheet credited to C. C. Colton this variation: "Examinations are formidable even to the best prepared, for the greatest fool may ask more than the wisest man can answer."—I am, etc.,

London, W.C.1. W. G. FOGLAND.

Nitrous Oxide in Dentistry

SIR,—The Treasurer of St. Bartholomew's Hospital has asked me to make known through your columns that the tests referred to on pages 132 and 164 of my book, *Nitrous Oxide in Dentistry*, were made in March, 1956, and that the machines at present in use at that hospital have been tested by the head of the department of anaesthesia and are functioning satisfactorily.—I am, etc.,

London, S.E.1. J. G. BOURNE.

POINTS FROM LETTERS

"O for a Beaker Full"

Dr. JOHN A. MCCLUSKIE (Sydney, Australia) writes: Dr. Richard Asher (June 18, p. 1895) with consummate boldness claims that Keats recognized that alcohol is an anaesthetic when he called: "O for a beaker full . . . " ["of the true, the blushful Hippocrene"]. His claim is audacious. Keats was surely referring not to alcohol but to a fountain of Mount Helicon sacred to Apollo and to the muses. The

fountain was originated by Pegasus, the winged horse, which was the embodiment of the power that raises a poet's imagination above the earth: hence Keats: "that I might drink and leave the world unseen." Dr. Asher is disappointing in his poetic mission.

Road Accidents

Dr. S. LANCASTER (Stallington Hall Hospital, Stoke-on-Trent) writes: If alcohol "accentuates these inherent tendencies" [impatience and showing-off], as Dr. D. W. Dryer states (July 2, p. 67), it is a cause of road accidents. My experience in casualties in a number of hospitals has been that road accidents come in soon after the public houses close more than at any other time. The answer, I believe, is partly education.

Wrong Prescription

Dr. L. G. JACOB (Bracknell, Berks) writes: Your remark in connexion with "librium" (July 23, p. 286) that "our neighbours, colleagues, competitors, and family seem all too often to be animated by a lynx-like ferocity" suggests a wonderful future for the drug. Lacing the breakfast coffee with it, and perhaps drinking tea oneself, would make the settlement of any controversy easy. Correspondence would not be so easy, unless the opponent responded to the sporting appeal, "Before writing this I took librium. Will you kindly do the same before answering?"

Treatment of Ulcerative Colitis

Dr. R. W. COCKSHUT (London, N.W.4) writes: In assessing the results of treatment of ulcerative colitis with steroids, at Oxford, since 1956 (July 9, p. 102), no account can be taken of the number of these cures which will develop carcinoma of the colon in the years to come, simply because they still have their colons. Why anyone, in the light of the known facts, should be exposed to this risk when the prevention is so obvious is beyond understanding.

High-pressure Salesmanship

Dr. H. J. PRATAP (Liverpool, 18) writes: Representatives of the drug firms and their publicity departments are paid to do their job, and there is no doubt they do their job very well, but are the members of the medical profession in the National Health Service doing theirs? Large quantities of proprietary preparations, including expensive antibiotics and steroids, are prescribed daily. If the general practitioners and the doctors in the hospitals exercised a certain amount of restraint and paused to think, and made more use of the *National Formulary*, I am sure they would prescribe preparations that are cheaper and equally effective. These would be less drain on the National Exchequer. What is more, the drug firms would not pester the doctors so much through their representatives or through the post.

Vitamin-E Therapy

Dr. V. R. O'CONNOR (Leamington Spa) writes: With reference to the issue of the *B.M.J.* (June 18, p. 1905) in which a doctor inquired in "Any Questions?", "What, if any, are the indications for vitamin-E therapy?" the reply was, "So far as man is concerned, it has never been conclusively proved that there is a specific disease which is due to deficiency of vitamin E and which can be cured by administration of the vitamin." I feel that, in the interests of clinical medicine and surgery . . . my few cases and publications should be brought to the attention of the profession.[1 2 3] . . . The foregoing should indicate that vitamin E is a valuable therapeutic agent. I am sorry to see it denigrated by someone who is apparently quite unfamiliar with the literature and with its use.

REFERENCES

1 O'Connor, V. R., *Med. Wld (Lond.)*, 1950, **72**, 299.
2 —— *Practitioner*, 1951, **166**, 171.
3 —— *Internat. Congr. (Venice) Bull.*, 1955.

*** This subject is discussed in "Notes and Comments" at page 618 of this issue.—ED., *B.M.J.*

Obituary

F. GARFIELD HODDER WILLIAMS, O.B.E.
LL.D., M.B., B.S.

Dr. F. Garfield Hodder Williams, Dean Emeritus of Manchester, and formerly well known for his work in the mission field, died suddenly in Devonshire on August 8. He was 78 years of age.

Frank Garfield Hodder Williams was born at Bromley, Kent, on November 21, 1881. One of his grandfathers was the founder of the publishing company of Hodder and Stoughton, and he was a great-nephew of Sir George Williams, who founded the Y.M.C.A. Educated at the City of London School, and St. Bartholomew's Hospital, he graduated M.B., B.S. in 1908. He once said that "the old Bart's was not the modern place it is to-day. Where I had my rooms the noise of meat carts going to Smithfield Market and of the postal vans going to St. Martin's-le-Grand made the night horrible and work even more than ordinarily difficult. But quite apart from that, a medical student's life then was, I imagine, as difficult as it is now." He believed that of all classes of people in the community the doctor most needed some hobby outside his profession, and this applied equally to the medical student—a hobby which had a certain cultural quality. He himself could relax when reading history.

He was not greatly attracted to the practice of clinical medicine, and, having held the post of London secretary of the Students' Christian Movement, he was appointed vice-principal of the science department of St. John's College, Agra, shortly after qualification as a doctor. In 1914 he was ordained in the Church of England and became principal of St. Andrew's College, Gorakhpur. For his work in the United Provinces of India during the first world war he was appointed O.B.E. in 1919.

Returning to England after the war, he became an assistant master at Rugby School for a short time, but left to become foreign secretary in charge of education for the Church Missionary Society. During the next few years he travelled widely, visiting Tibet, Abyssinia, tropical Africa, and the North-West Frontier of India. In 1929 he became Dean of Llandaff, and two years later he was appointed Dean of Manchester and Rector of the Cathedral, succeeding Dr. Hewlett Johnson. He retired from the deanery in 1948, and in recent years he had been living in Devonshire. In 1950 he was appointed to a canonry in the diocese of Central New York, an unusual honour for an English clergyman.

Tall, thin, distinguished in appearance, kindly, forthright, and extraordinarily good company, Garfield Williams was one of the best Deans that Manchester has had. He was a member of the board of management of the Manchester Royal Infirmary from 1933, becoming a member of the board of governors when the National Health Service came into being. In committee he was a man of outstanding clearness of vision and by no means a "yes man." He was always provocative and probably deliberately so. Certainly his presence was a great asset to the board and valued highly by both lay and medical members.

His life's work was in the Church. He was an incisive, persuasive, and popular preacher. He took keen interest in the music of the services, and in consequence it reached a particularly high standard. But his greatest work was in the reconstruction of the bomb-damaged cathedral. This lovely 15th century building suffered more damage than any other cathedral except that of Coventry. The Dean, staying in an adjacent hotel, witnessed the dreadful scene. With courage and determination to save his cathedral, he gave his personal devotion and encouragement to architect, builders, and workmen, a task that might have broken a lesser man. All reacted to his infectious enthusiasm. At first it was a question of propping to save collapse at many points, and then came the careful thought and planning necessary to make the wreck of a beautiful old church into

a cathedral once again. He was responsible for the early stages of the work that took fourteen years to complete. This work is his abiding monument.

Dr. Garfield Hodder Williams is survived by his widow, a son, and two daughters.

J. A. INNES, M.B., Ch.B., B.Sc., M.R.C.P.

Dr. John A. Innes, who practised in Aberdeen for more than 40 years and was formerly physician to the Royal Infirmary there, died on July 30, aged 67.

John Alexander Innes, the son of a doctor, was born on November 28, 1892, and educated at Robert Gordon's College and Aberdeen University, where for a time he was senior assistant in the physiology department. He graduated B.Sc. in 1913 and M.B., Ch.B. (with distinction) in 1915. During the first world war he served in the R.A.M.C. on the Salonika front until he was recalled to take over his father's practice in Aberdeen. In 1923 he was appointed assistant physician in the Aberdeen Royal Infirmary, and soon afterwards he gained the M.R.C.P. of London. From 1933 to 1937 he was a physician in charge of wards in the hospital, and at the University of Aberdeen he was a lecturer in clinical medicine. He was chairman of the Aberdeen City Division of the B.M.A. in 1936–7.

G. G. B. writes: John Innes and I started medicine together, and in the early days of the first world war we were unqualified residents during our final year. In after years he was to become my colleague in hospital and my doctor. A dynamic personality, he had more than his own share of brains and was well known in the North of Scotland as an outstanding member of his profession. He had a direct approach to most things, hating cant and insincerity. His friends were legion. He lived intensely. He was far too human "to scorn the delights and live laborious days." The glittering prizes of surgery and medicine were not for him. Among his manifold interests were music, golf, and photography, but he was at his happiest when he escaped from town to fish for salmon in the gathering dusk of a summer's night at Cairnton on the river Dee, or to wander along the banks of the Deveron at Huntly Lodge waiting for the trout to rise. However, no man can banish all his cares, and at times John Innes must have found life hard and unrelenting. He could see further into the future than most people, and he had no illusions. He knew that the lodestar of every life is remote and unattainable—to be what we cannot be. Yet the happy days we knew might be described in the words of Viscount Grey of Falloden "as not less bright because they are lit in memory by the light of a setting sun."

E. H. GRUBBE, M.D., F.A.C.P.

Dr. E. H. Grubbe, the last survivor of a group of pioneers in radiology in the United States of America and one who claimed to be the first to show tissue damage from Roentgen rays, died in Chicago on March 26. He was 85 years of age.

Emil Hermann Grubbe was born in Chicago, of Swiss-German parents, on New Year's Day, 1875. After a training in chemistry and physics, he set up, when only 19 years old, as an assayer of rare metals, and soon gained a reputation for accuracy and honesty which were characteristics of his life throughout. In his book, *X-ray Treatment, Its Origin, Birth, and Early History*, Grubbe described how he discovered platinum in ores gathered in an Indian reservation at Cripple Creek, Idaho. He was soon the possessor of large stocks of the metal, for which the only use in those days was in the making of leading-in wires for vacuum tubes. So, as he wrote, "I had to go into the vacuum tube business to use up my platinum." It was while testing his Crookes tubes that Grubbe received the first of his *x*-ray burns. In 1895 he was teaching physics and chemistry in a medical school and taking the medical course himself. He was licensed to practise in 1898, but did not gain his M.D. until later. In 1896 he designed, assembled, and operated at the Hahnemann Hospital the first *x*-ray apparatus in Chicago. It was with this instrument and in that year that he carried out *x*-ray treatment on a recurrent carcinoma of the breast—probably the first occasion on which *x* rays were applied therapeutically. He did so at the request of one of the physicians who had seen Grubbe's burns and who advanced the idea that a physical agent capable of producing such a violent reaction in healthy tissue might be potent if used in the treatment of disease.

From then onwards Grubbe devoted his time and ingenuity to *x*-ray therapy. He became the first teacher in radiology in the faculty of the Illinois College of Electrotherapeutics when it decided to add "and *X*-rays" to its title. His laboratory in the Hahnemann Hospital also became the nucleus of the first department for teaching the subject to medical students. His whole life was afflicted with mounting disabilities resulting from overdosages of *x* rays to various parts of his body during his early experiments, and he had a succession of surgical amputations and tumour removals. The ninety-second operation was performed on him as recently as 1959. But his desire to contribute towards the advancement of medical science through radiology, and particularly in the treatment of cancer, remained till the end of his life.

Honorary awards were conferred on him by the American Institute of Medicine, the Walter Reed Society, the Chicago Roentgen Society, the American Cancer Society, and the Chicago Medical Society. He was a founder member of the Roentgen Society of the United States, later the American Roentgen Ray Society. A Fellow of the American College of Physicians, he was a past-president of the National Society for Physical Therapeutics. In his will Dr. Grubbe established "The Emil H. Grubbe Radiation Therapy Foundation of the University of Chicago." He also provided for a Gold Medal to be awarded annually by the Chicago Medical Society and another by the Radiological Society of North America.

ARCHIBALD ROMANES, M.D.

Dr. Archibald Romanes, who practised in Ilford for nearly forty years, died in hospital there on July 26. He was 72 years of age.

Archie Romanes was born in Dunfermline in the Kingdom of Fife on May 22, 1888, and received his early education at Dunfermline High School. He went on to Edinburgh University, where he graduated M.A. in 1908 and M.B., Ch.B. in 1912. After holding the post of house-surgeon in the Edinburgh Royal Infirmary, he went to the Sheffield Royal Infirmary as a house-physician. His next appointment was to the Municipal Hospital, Neasden, where he became assistant medical superintendent. He joined the R.A.M.C. in 1915, and, with the rank of captain, saw service in France from 1916 onwards. He was stationed with the Army of Occupation at Cologne during the outbreak of typhoid fever there in 1919, and the experience gained in that epidemic formed the basis for a thesis for his M.D., which he gained later that year. After demobilization, he joined the late Dr. Houchin at Ilford, succeeding to the practice shortly afterwards and remaining there until his retirement in 1956. He filled the office of president of the Ilford Medical Society for two terms, and was chairman of the Stratford Division of the B.M.A. in 1937–8.

Dr. Romanes was greatly loved by his patients, was held in high esteem by his colleagues, and was considered by the consultants on the staff of the local hospitals as one of the most able practitioners in the area. His knowledge of medicine was wide, and he never spared himself where the interests of his patients were concerned. He was a quiet man, never seeking the limelight, enjoying the company of his family, enjoying his reading and his golf, and during the last few years of his life enjoying his garden, which he had laid out so beautifully.

He is survived by his wife and two married daughters, to whom we extend our deep sympathy.—A. F.

A. G. VARIAN, M.A., M.D.

The obituary of Dr. A. G. Varian was printed in the *Journal* of July 16, p. 238.

B. A. S. writes: By the sudden death of Dr. George Varian Totnes has lost not only a most skilful practitioner, but a well-loved friend. For a number of years he carried on a most successful practice in Hertfordshire, then came with his family to Devon in 1929. Here he found much fresh material for his professional skills. He was instrumental in reorganizing the Cottage Hospital in Totnes, and for twenty years he was able to perform outstanding surgery as well as carrying on his most successful general practice. In his work he allied clinical acumen of a very high order with boundless energy and inevitably acquired an enviable reputation in the best family-doctor tradition. In 1952 he was struck down by ill-health, but he did not spare himself, and in spite of the onset of a cardiac condition, which ultimately caused his death, he returned to his work, and for eight years continued to administer his practice. His charming manner and his native sense of humour endeared him to all who knew him, and by them he will be remembered with affection and gratitude, but most of all by his widow and young daughter.

Medico-Legal

SUICIDE AND THE FATAL ACCIDENTS ACT

[FROM OUR LEGAL CORRESPONDENT]

At Common Law it used not to be a tort, or civil wrong for which compensation could be claimed, to cause the death of another. This rule, however, has been encroached upon by the Fatal Accidents Act, 1946, which provides that

"Whensoever the death of a person shall be caused by wrongful act, neglect, or default, and the act, neglect, or default is such as would (if death had not ensued) have entitled the party injured to maintain an action and recover damages in respect thereof, then and in every such case the person who would have been liable if death had not ensued shall be liable to an action for damages, notwithstanding the death of the person injured, and although the death shall have been caused under such circumstances as amount to a felony."

The action lies at the suit of the executor or administrator of the deceased for the benefit of certain relatives, if they have suffered damage by the death.

Proximate Cause of Death

The death in question may be the result of suicide caused by some unbalancing of the mind or melancholia arising out of an accident caused by the defendant. Assuming a sufficient causative link between the act of the defendant and the suicide of the deceased, can an action be brought in respect of the death, bearing in mind the rule of common law that no person can obtain or enforce any rights resulting to him from his own crime, nor can his personal representative claiming under him enforce those rights[1]? If the deceased was fully sane at the time of his suicide, the personal representatives cannot sue in respect of the death, as there is a *novus actus interveniens* and the death is not the proximate result of the act of the defendant. If the deceased was legally insane at the time of his suicide, he is excused from the guilt of his crime and his representatives can sue in respect of his death. But difficulty arises where the deceased was "medically" but not legally insane at the time of his suicide. In that case the death could be a proximate result of the defendant's act and yet still be a crime. In New Zealand[2] it has been held that in this last case there could be no action under the Fatal Accidents Act.[2] However, the better view would appear to be that such an action will lie, and it is open to the English courts so to find, in view of the closing words of Section 1 of the Act, which allow an action even though the death was caused in circumstances amounting in law to a felony.

Award to Widow

On June 16, at the York Assizes, £500 was awarded to a widow under the Fatal Accidents Act in respect of her claim for the death of her husband, aged 65 (*The Journal*, June 17). He had committed suicide by slashing his wrists after an accident at his place of work which resulted in a change of temperament. Mr. Justice Davies found that the deceased had a predisposition to mental illness, and on the balance of probability that illness (which carried a grave suicidal risk) was triggered off by his accident. It does not appear from the report of the case whether the court found Mr. Todd to be legally insane at the time of his suicide.

[1] *Brit. med. J.*, 1960, **2**, 399.
[2] *Murdoch v. British Israel Federation* [1942] N.Z.L.R. 600.

LUNG CANCER AND TOBACCO FIRMS

[FROM OUR LEGAL CORRESPONDENT]

Following close upon Mr. Pritchard's action against the Liggett and Myers Tobacco Company (*Journal*, August 6, p. 474) a further action in respect of cancer has been tried against the American Tobacco Company (*The Times*, August 4).

Before a Federal jury at Miami, Florida, the widow of the late Mr. Edwin Green sued for $1,500,000 from the American Tobacco Company, the manufacturers of Lucky Strike cigarettes. Mr. Green died in 1958 at the age of 49 as a result of lung cancer diagnosed in 1956. Evidence was given that for thirty years before 1956 Mr. Green had smoked between 40 and 60 Lucky Strike cigarettes daily.

This case is believed to be the first of its type where there has been held to be sufficient evidence to go to the jury. In answer to specific questions, the jury found that Mr. Green had cancer of the lung, and that this was the cause of his death. Moreover, in striking contrast to the Pritchard Case, the jury found that the lung cancer was caused by smoking Lucky Strike cigarettes. However, the jury also held that, at the time the cancer was contracted, the danger from cigarettes was not sufficiently known for the manufacturers to be liable. To be liable in negligence, it must be shown that one knew or ought to have known of the danger one was creating.

It does not appear from the brief reports at present available whether the defendant company raised any of the defences referred to in our comments on the Pritchard Case.

FORCIBLE REMOVAL TO MENTAL HOSPITAL

[FROM OUR LEGAL CORRESPONDENT]

On May 25 the Court of Appeal affirmed the leave granted to Mr. Henry Buxton and his wife Mrs. Annie Buxton, of Hayes, Middlesex, under Section 330 of the Lunacy Act, 1890 (as amended by Section 16 of the Mental Treatment Act, 1930), to take proceedings against Mr. Eric M. Jayne, of Havant, Hampshire (*The Times*, May 20). Mr. Jayne was formerly a duly authorized officer employed by the Middlesex County Council under those Acts. Section 330 of the Lunacy Act, 1890 (as amended), protects persons acting in pursuance of the Lunacy and Mental Treatment Acts from litigation. No civil or criminal proceedings can be commenced upon such matters without the leave of the High Court, and leave will not be granted unless the court is satisfied that there is substantial ground for the contention that the person against whom it is sought to bring proceedings has acted in bad faith or without reasonable care.

Mrs. Buxton, who was then 57, became severely emotionally upset on January 10, 1959, by a domestic dispute. In her doctor's view she required observation, psychiatric treatment, and skilled attention which she would not get at

home. Mr. Jayne gave evidence that Mrs. Buxton was greatly disturbed, acting in an abnormal manner and highly excited. In his view the only sensible and proper step was to remove her to hospital for her own protection, so that she could be properly looked after. On that morning she was so removed, and was placed in an observation ward. There was no evidence that Mrs. Buxton was, or was believed to be, of unsound mind.

There was no suggestion in this case of bad faith, so that leave to bring proceedings could not be granted on this ground. The Court of Appeal, however, held that on the authorities the duly authorized officer must have reasonable ground for believing that the person was of unsound mind: hence the question arose whether Mr. Jayne had acted without reasonable care. The absence of any evidence that Mrs. Buxton was of unsound mind gave ample support for the contention that Mr. Jayne had acted without reasonable care. Leave to bring proceedings was therefore granted.

Whether Mr. Jayne did in fact act without reasonable care is a matter to be decided at the trial of these proceedings.

PRELUDIN APPLICATION

[FROM OUR LEGAL CORRESPONDENT]

An application to the Court of Criminal Appeal, based on a plea that the convicted applicant was influenced by "preludin" at the time of the crime, was dismissed on July 11.[1]

Miss Johanna Ehrenstrasser applied for leave to appeal against a sentence of 12 months' imprisonment imposed on her in March for larceny, and for leave to call further evidence to show that her symptoms at the relevant time were consistent with her having taken large doses of preludin.

The applicant had pleaded guilty at the trial. The grounds for this application were that the trial judge refused to accept the submission that the applicant had been taking preludin in very large doses, and it was proved to be dangerous in large doses. Medical evidence had been given in mitigation at the trial to the effect that the applicant's conduct was consistent with taking preludin, and that the drug was extremely dangerous and if taken in excessive doses resulted in confusional insanity or even suicidal tendencies. At the relevant time preludin was on sale without prescription. Since sentence in this case, it has been put on the poisons list.

The refusal of this application did not involve any failure by the court to accept the medical evidence. The court stated in their judgment that, even accepting the fresh evidence which the applicant wished to call, in the circumstances of the case the sentence could not be criticized: the applicant had pleaded guilty to four offences of larceny, eleven other offences had been taken into account, and the property involved was worth £6,900.

NULLITY DECREE AFTER CONCEPTION

[FROM OUR LEGAL CORRESPONDENT]

On July 11 Mr. Justice Collingwood granted a decree of nullity to a wife on the ground of her husband's incapacity, despite the fact that the wife had borne a child by him.[2] The parties were married on July 1, 1950. Before marriage the husband told his wife that he could give her only a funny sort of love, but he would do his best. On several occasions after marriage the husband attempted intercourse, but on each occasion failed because of ejaculatio praecox. In January, 1954, the husband attempted intercourse with the same result, but three months later the wife found she was pregnant, and on November 7, 1954, gave birth to a child. After the birth the husband made no further attempts at intercourse and the parties separated in April, 1959. The husband alleged that the child was conceived after normal intercourse, but the wife said that the conception was the result of fecundatio ab extra. The wife's evidence was supported by her family doctor, who stated that, even after conception, gynaecological exploration of the wife was unusually difficult.

The court preferred the evidence of the wife to that of the husband, and held that the marriage had never been consummated owing to the incapacity of the husband *quoad hanc*. The wife was granted a decree nisi of nullity and custody of the child.

The possibility of fecundatio ab extra is well known to the courts, and though the occurrence is unusual there have been previous reported cases where a decree of nullity has been granted in such circumstances.

[1] *The Times*, July 12.
[2] *The Times*, July 12.

EVIDENCE BY TAPE-RECORDER

[FROM OUR LEGAL CORRESPONDENT]

The use of tape-recorders for the purpose of preserving evidence is growing, and the admissibility of such evidence is clearly a question of great importance. In a recent Scottish case the Scottish Court of Criminal Appeal upheld the use of such evidence in the trial of a blackmailer.[1]

A man complained to the police that he was being blackmailed by the threat of disclosure to his employers that he had been convicted for embezzlement. He was supplied by the police with four marked £1 notes, a small microphone, which was concealed in his lapel, a crystal-controlled transmitter, which he carried in a pocket, and batteries carried in the other pocket. He then met the blackmailer in the public part of a railway station, and their conversation was transmitted to a receiving set in a private room at the railway station, where a police officer heard it and recorded it by tape-recorder. Other policemen saw the blackmailer and his victim engaged in conversation, and, when they arrested the blackmailer, found the marked £1 notes on him.

The blackmailer and a partner in crime were convicted and subsequently appealed on the ground of inadmissibility of evidence: it was said on their behalf that the evidence was secondhand and merely an interpretation of a recorded conversation. On June 8 the appeal was dismissed. So far as the listening policeman was concerned, the tape-recording was as much evidence as if he had taken shorthand notes of the conversation. The court did, however, disallow the evidence of a stenographer who later transcribed the tape, on the grounds that she was not expert in this type of transcription.

Tape-recordings are used in England, as well as in Scotland, in both criminal and civil proceedings. Subject to the usual laws of evidence, they are perfectly admissible: the hearsay rule, for instance, shuts out much evidence of what persons have said, whether that evidence be supported by tape-recordings or not. There are, however, certain technical difficulties which make it necessary in most cases that a witness should be called who heard the whole of the conversation while he was recording it: the parties speaking must be clearly identified, and the possibility of the tape having been tampered with must be ruled out. Moreover, tape-recordings are often indistinct, and their transcription is a matter for an expert who is able to give an authoritative interpretation of the noises on the tape. The advisers of the other party to the litigation must be given an opportunity of hearing the tape so that they may challenge or agree with the transcription. Above all, the conduct of the conversation recorded must be fair. Recordings of this sort are always open to the comment that one party knew he was talking for the record while the other did not. Any suggestion of putting words into that person's mouth, or of colouring his words by the other half of the conversation, will deprive a recording of all weight, whether or not it is strictly admissible.

[1] *Hopes and another* v. *H.M. Advocate*, 1960, *Scots Law Times*, 54

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on July 30 the degree of B.M. was conferred on G. H. Foster and P. Howard.

The Medical Scholarship for 1960–1 has been awarded to Walter George Bradley, Scholar of Worcester College; the Theodore Williams Scholarship in Anatomy for 1960 to David Frederick Horrobin, Scholar of Balliol College; and the Radcliffe Scholarship in Pharmacology to J. R. Hampton (Magdalen College).

UNIVERSITY OF EDINBURGH

At a Graduation Ceremonial on July 20 the Lawrence Poole Prize in Rehabilitation after Poliomyelitis was awarded to Professor Joseph Trueta, Nuffield Professor of Orthopaedic Surgery in the University of Oxford, and the Cameron Prize in Practical Therapeutics was awarded *in absentia* to Professor John Franklin Enders, Professor of Bacteriology and Immunology in the University of Harvard, for his work on growing the virus of poliomyelitis and other studies in viruses.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

On August 4 Professor Leslie N. Pyrah was elected a Member of the Council of the College. The result of the poll was as follows: *Elected*, Professor Leslie N. Pyrah (409 votes). *Not elected*, the figures in parentheses indicating the number of votes polled, Mr. E. G. Muir (311), Mr. N. L. Capener (275), Mr. N. R. Barrett (273), Mr. David Trevor (262), Professor A. M. Boyd (195), Mr. A. H. Hunt (137), Mr. E. C. B. Butler (131), Mr. George Qvist (109), Mr. R. W. Raven (103), Mr. D. N. Matthews (102), Mr. D. Ioan-Jones (50), Mr. G. H. Macnab (37).

In all 2,409 Fellows voted, and in addition nine votes were found to be invalid.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College held on July 22 with the President, Professor John Bruce, in the chair, the honorary Fellowship was conferred on Professor J. W. Hinton, professor of surgery in the New York Postgraduate Surgical School.

The following candidates were admitted Fellows without examination: J. W. T. Dixon and A. G. Smith.

At the same meeting, the following candidates, who had passed the requisite examinations, were admitted Fellows:

S. V. Bhave, B. J. Carew, V. P. Chadha, S. L. Cooke, J. N. Cozens-Hardy, J. R. M. Davidson, A. B. R. Desai, L. J. De Souza, A. Dev, M. S. G. Douglas, R. K. Dutta, H. N. P. Dwivedi, T. A. English, Guan Swee William Fung, S. K. Ghai, J. R. P. Gibbons, J. I. H. Hadfield, B. H. Helal, S. El D. H. Hosny, M. A. Hossein, I. Jacobson, G. S. Joss, N. Kollitsis, R. A. MacMahon, W. M. McQuillan, K. K. Madhavan, A. M. Mehta, G. P. Mohanty, M. H. W. Mullerworth, Maung Sein Myint, M. F. Porter, D. J. Reid, G. R. Roberts, R. A. Roxburgh, M. B. H. Sammour, D. P. Sanan, L. P. Scimon, R. J. Shah, Mary P. Shepherd, G. D. Singhal, G. G. Smit, D. W. Smith, H. C. Smith, M. V. S. Valiathan, R. E. Vance, W. Waldie, D. F. Weinman, C. F. A. Whelan, D. P. C. Williams, M. Y. Wipat.

Vital Statistics

Occupational Morbidity

The illnesses that bring a patient to his family doctor have been studied in relation to the patient's occupation and social class by about 120 general practitioners in England and Wales. The results, analysed by the General Register Office, were published last week (*Morbidity Statistics from General Practice*, Volume 2 (Occupation), by W. P. D. Logan, M.D., Ph.D. H.M.S.O., 25s. net). The statistics recorded are based on the numbers of consultations between patient and doctor. Consequently they are not a direct measure of morbidity, because people in different occupations may feel differently inclined about consulting their doctor for the same disease, or have different opportunities to do so.

The figures for male patients at work show the following trends:

Respiratory Tuberculosis.—In contrast with mortality, there was no social-class gradient.

Malignant Neoplasms.—Ratios were low for agricultural workers, mine workers, and shop assistants, and exceptionally high for men in personal service.

Psychoneuroses.—A diminishing gradient from high rates in social class 1 to low in social classes 4 and 5. Farmers had low rates and professional workers, clerks, and foremen high rates.

Otitis Media.—A rising gradient from social class 1 to 5. Mine workers had the highest rate.

Coronary Disease.—In contrast to the social-class gradient of mortality there was none of morbidity. Groups with high ratios were shopkeepers, clerical workers, and foremen; groups with low ratios were mine workers and agricultural workers.

Common Cold.—Mine workers had a rate almost three times the average for all men. They also had the highest rates for acute pharyngitis, acute tonsillitis, and influenza.

Peptic Ulcer.—A steep ascending gradient from social class 1 to 5. All manual workers had rates above average, particularly foremen and transport workers. Groups with low rates included farmers and higher professional workers.

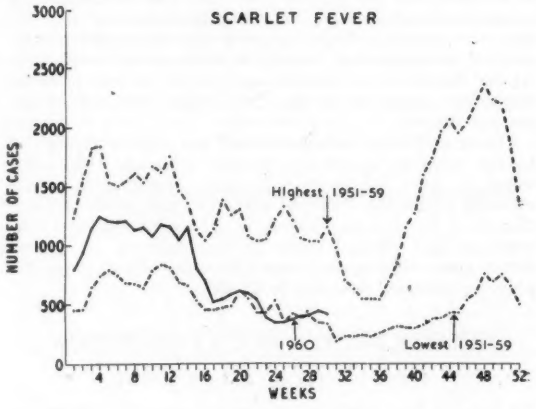
Arthritis and Rheumatism.—A rising gradient from social class 1 to 4 and 5. Mine workers had the highest rate and low rates were recorded for agricultural workers, professional men, and shopkeepers.

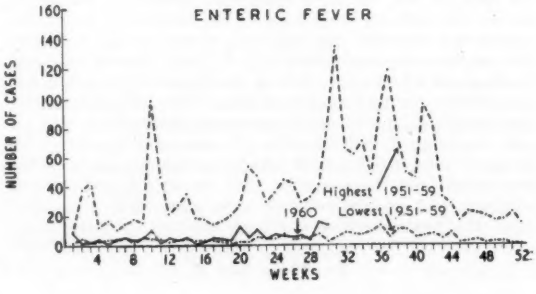
Non-sickness.—A descending gradient from social class 1 to 5, except that mine workers had the highest rate.

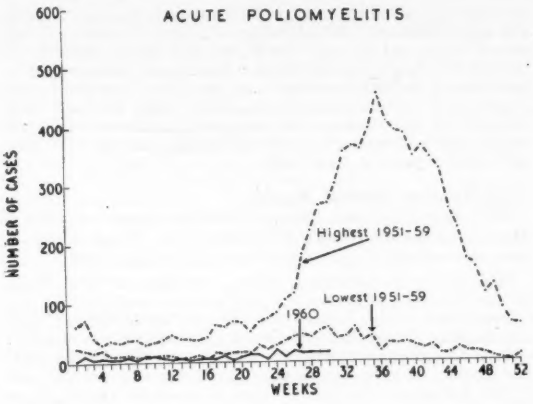
As regards women, the rates for those in agricultural occupations were below average while those in non-manual occupations had rates above average. The rates for women classified as housewives were slightly below average.

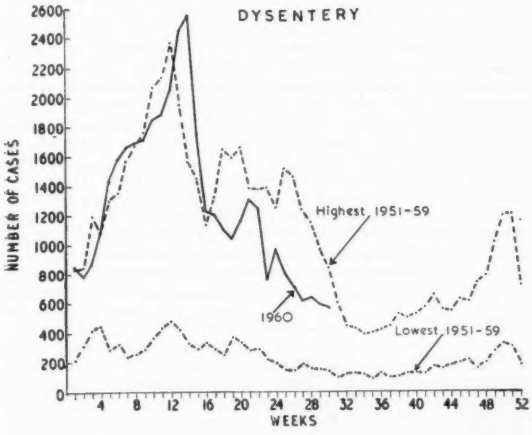
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending July 30	Week Ending Aug. 6
Measles		
Lancashire	810	**782**
Liverpool C.B.	210	**208**
Manchester C.B.	101	**96**
Dysentery		
Lancashire	68	**69**
Liverpool C.B.	15	**18**
London	91	**54**
Yorkshire West Riding	75	**73**
Leeds C.B.	20	**17**
Dearne U.D.	5	**26**
Glasgow	80	**59**
Food poisoning		
London	31	**26**
Wandsworth	5	**10**
Lancashire	30	**38**
Liverpool C.B.	12	**26**
Glamorganshire	32	**36**
Cardiff C.B.	29	**0**
Cowbridge R.D.	0	**32**
Glasgow	9	**114**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 30** (No. 30) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	1	0	1	6	3	6	0	1
Dysentery	566	91	118	8	5	398	43	160	23	9
Encephalitis, acute	2	0		0		6	0	0	0	
Enteric fever:										
Typhoid	2	0	2	0	1	0	0	0	0	3
Paratyphoid	12	5	4(B)	0		3	1	0	0	
Food-poisoning	222	31	57	2		293	40	63	3	
Infective enteritis or diarrhoea under 2 years				17	22				10	43
Measles*	2,856	139	66	2	4	6,092	133	110	141	95
Meningococcal infection	17	0	15	2		13	1	6	0	
Ophthalmia neonatorum	21	2	3	0		17	3	7	0	1
Pneumonia†	131	5	96	0		146	12	105	7	
Poliomyelitis, acute:										
Paralytic	7	1	0	1	8	35	6	3	0	
Non-paralytic	9	2	0			23	9	1		
Puerperal fever§	173	30	10	1	1	207	33	9	0	
Scarlet fever	429	19	41	10	17	627	31	48	9	20
Tuberculosis:										
Respiratory	409	44	60	11		451	74	54	4	
Non-respiratory	65	6	12	0		64	6	10	0	
Whooping-cough	1,389	149	142	11	37	677	21	61	35	96

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	3	1		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	1	0	1	2	0	0	0	0
Influenza	4	0	0	0	0	2	2	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	389	40	13	9	4	298	24	17	1	6
Poliomyelitis, acute	1	0		0	2	4	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	53	1	8	0	2	57	6	3	0	2
Non-respiratory		1	0	1	0		0	1	0	0
Whooping-cough	0	0	1	0	0	0	0	0	0	0
Deaths 0–1 year	308	27	22	7	16	266	24	34	13	5
Deaths (excluding stillbirths)	8,672	681	518	100	143	7,677	572	495	122	119
LIVE BIRTHS	15,832	1350	1014	298	503	14,687	1256	1061	277	355
STILLBIRTHS	288	29	17			302	28	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

M.R.C. Travelling Fellowships in Medicine

The Medical Research Council have made the following appointments to Travelling Fellowships in medicine to be held in the United States of America for the academic year 1960–61:

Rockefeller Travelling Fellowships, Dr. D. N. BARON (honorary consultant chemical pathologist, Royal Free Hospital) to the Ben May Institute for Cancer Research, University of Chicago; Dr. C. J. DICKINSON (Leverhulme Research Scholar) to the Cleveland Clinic Foundation; Dr. R. W. GUILLERY (lecturer, anatomy department, University College, London) to the University of Wisconsin; Dr. J. W. S. HARRIS (lecturer, department of anatomy, London Hospital Medical College) to the Carnegie Institution of Washington; Dr. E. W. POOLE (lecturer, department of clinical neurophysiology, Institute of Psychiatry) to the Johns Hopkins University, Baltimore, Maryland; Dr. P. H. WRIGHT (lecturer in chemical pathology, Guy's Hospital Medical School) to the department of medicine, University of Chicago. *United States Public Health Service Fellowships,* Dr. H. KEEN (lecturer and research fellow, department of experimental medicine, Guy's Hospital, London) to the National Institutes of Health, Bethesda; Mr. S. J. KILPATRICK (lecturer in medical statistics, department of social and preventive medicine, The Queen's University, Belfast) to the Statistical Laboratory, Iowa State College; Dr. J. D. H. SLATER (medical registrar, department of medicine, Postgraduate Medical School of London) to the Presbyterian Hospital, New York; Dr. W. C. WATSON (senior registrar, University Medical Unit, Glasgow Royal Infirmary) to the National Heart Institute, Bethesda. *Lederle Travelling Fellowship,* Dr. CELIA M. OAKLEY (registrar, department of medicine, Hammersmith Hospital) to the Strong Memorial Hospital, Rochester. *Lilly Foreign Educational Fellowships,* Dr. M. T. HARRISON (registrar, department of medicine, Hammersmith Hospital) to the Johns Hopkins Hospital, Baltimore. *Alexander Pigott Wernher Memorial Travelling Fellowship in Ophthalmology and Otology,* Dr. A. B. LEITH (resident, Montreal General Hospital) to the Institute of Ophthalmology of the University of London; Mr. C. I. PHILLIPS consultant ophthalmic surgeon to United Bristol Hospitals and to South-western Regional Hospital Board) to the Massachusetts Eye Infirmary and Harvard Medical School.

Deposition of Strontium-90 after the Windscale Accident

"The Deposition of Strontium-89 and Strontium-90 in Agricultural Land and their Entry into Milk after the Reactor Accident at Windscale in October, 1957" is the title of a report issued this week by the United Kingdom Atomic Energy Authority and the Agricultural Research Council (H.M.S.O. Price 5s. net). It records the results of studying the deposition of strontium-90 on farm land at different distances from the Windscale works and its concentration in milk. On farms within two miles of the works the deposition of strontium-90 was on average 160 millimicrocuries per square metre: the value expected from fall-out from weapon tests would have been 10 to 15 mμc per square metre. The mean content of strontium-90 in milk from the farm which showed the highest deposition figure was 7% of the maximum permissible level recommended by the Medical Research Council for use after reactor accidents. On the farms studied at greater distances from the works, fall-out from weapon tests was the major source of the strontium-90 on agricultural land. Contamination of milk was predominantly, if not entirely, due to recent fall-out from weapon tests. Further reference to these findings will be made in a later issue of the *Journal.*

World Federation for Mental Health

The World Federation for Mental Health held its thirteenth annual meeting in Edinburgh—under the presidency of Professor PAUL SIVADON—in the week beginning August 8, and more than 500 delegates from 42 different countries were present.

The theme of the meeting was "Action for Mental Health" and the agenda was designed around the six main areas of activity of the World Mental Health Year: the mental health needs of children; cross-cultural surveys of mental disorder; teaching the principles of mental health in professional training; mental health and industrialization; the psychological aspects of migration; and mental health and old age. Sir DAVID HENDERSON, president of the Scottish Association for Mental Health, said that an exciting new field of research lay ahead, and the causes, prevalence, and treatment of nervous and mental illnesses might gradually yield up some of their secrets. A transatlantic discussion on world mental health problems was held during the week by submarine cable with a panel in New York.

Anglo-German Medical Society

The Anglo-German Medical Society held its Annual Meeting in Stuttgart on July 30 and 31. Three half-days were devoted to a symposium on medical education.

Professor J. S. MITCHELL, F.R.S., President of the British Section, opened a discussion on undergraduate teaching. He was followed by Professor SCHOEN (Göttingen) who stressed the value still attached in Germany to formal systematic lecture courses, and the difficulties in the way of a liberalization of the curriculum. The training of specialists in the Federal Republic was outlined by Dr. RHEINDORF (Frankfurt), whose expositions led to a lively discussion. Many speakers were impressed by the need for qualifying examinations corresponding to the M.R.C.P. and F.R.C.S. At present a specialist is registered after a period of training at one or more approved centres, and he may not qualify in more than one specialty; the acquisitions of higher degrees is thus rendered virtually impossible. The chief difficulty encountered in this simple method of specialist registration is the maintenance of a high and uniform standard throughout the West German Republic. Professor Dr. SCHARPFF (Stuttgart) gave an account of the organization of hospitals in the Federal Republic, which was reciprocated by an explanation of the National Health Service by Professor C. M. FLEMING (Glasgow). Professor Dr. H. BENNHOLD (Tübingen), President of the German Section, opened the discussion of this section. The German members were impressed by the good relations existing between doctors and administrators in the N.H.S. but doubted whether such a system would be successful in the different environment of the Federal Republic. The "economic miracle" in Germany has led to a similar shortage of nurses and auxiliaries as is experienced in Britain. The need for experimentation with home-care units, self-service wards, etc., was emphasized. Next year's meeting will be held in London (September 28–30) and will include a symposium on "Drug Action and Modern Therapy."

The first number of the Society's official organ, the bilingual *Anglo-German Medical Review,* was distributed at the meeting, and the full text of the symposium will be included in the second number. The *Review* is free to members of the Society, but inquiries about subscription rates should be sent to the publishers, Friedrich-Karl Schattauer-Verlag, Stuttgart, Germany.

New Ophthalmic Hospital, Jerusalem

The new Ophthalmic Hospital of the Order of St. John of Jerusalem is to be opened on October 11 by H.M. King HUSSEIN in the presence of the Grand Prior, H.R.H. the Duke of GLOUCESTER. (An annotation is printed on p. 591 of this week's *Journal.*)

[I. M. Graham. Photographers

The new Ophthalmic Hospital, Jerusalem.

Hospital Building Costs

Hospital design and construction is to be investigated by the Building Research Station with a view to lowering the cost of building hospitals, and a programme of research

is now being arranged with the Ministry of Health and the Department of Health for Scotland.

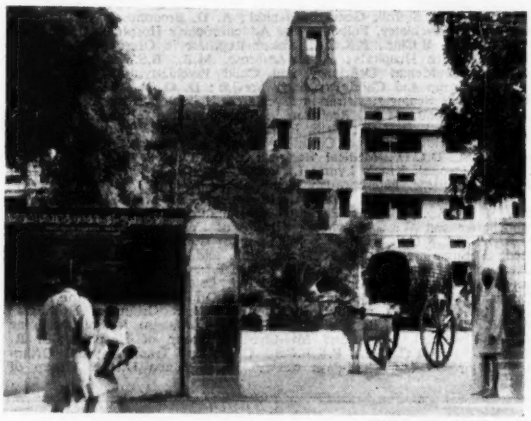
Government expenditure on hospitals may amount to £300m. over the next six or seven years, and there is much scope for research in this field. The Station will study ways of providing more economically engineering services in hospitals—heating and ventilation, operating theatre services, lighting, etc.—which can amount to a third of the total building cost. Studies will also be made of recently constructed hospitals to see if building costs can be cut in other ways. It should be possible, says the report, to pick out anomalies in building costs between different hospitals of similar capacity and to trace their causes. (*Building Research, 1959*, published for D.S.I.R. by H.M.S.O. Price 7s., by post 7s. 6d.)

Prisons Commissioners' Report

The research work described in the *Report of the Commissioners of Prisons for the Year 1959* (H.M.S.O., 9s. 6d. net) includes a social and psychological study of homosexuality by Birkbeck College; research by the Institute of Psychiatry on the psychological characteristics of various classes of prisoner compared with those of non-criminals; a comparison of the mental characteristics of murderers with those of other serious offenders which is being carried out at Broadmoor and in certain prisons; and a study by visiting psychiatrists from the Maudsley Hospital and the psychiatric social worker at Brixton of the use of bail or custody for men remanded for psychiatric reports, where the offences were similar. The report states that the general health of inmates in 1959 was well maintained.

Jubilee of Christian Medical College, Vellore

The Christian Medical College, Vellore, in South India, is celebrating the diamond jubilee of its hospital and the golden jubilee of its school of nursing during August, when it is hoped that the President of India, Dr. RAJENDRA PRASAD, will inaugurate the celebrations. A Jubilee Fund will be



["*Friends of Vellore*"

Entrance to Christian Medical College, Vellore.

set up, part of which will be used to build a permanent school of nursing and a dormitory for male interns.

The College was founded by the late Dr. IDA SCUDDER, granddaughter of the first American Missionary to India, who went to India in 1900. She died on May 24 this year in her ninetieth year. (See *Journal*, June 18, p. 1899.)

Maccabaean Prize and Medal

Through the generosity of the Maccabaeans—a primarily Jewish professional society founded in 1891—the Faculty of the History of Medicine and Pharmacy of the Worshipful Society of Apothecaries is able to offer an annual prize of not less than 25 guineas, with a bronze medal, for the best original essay on a subject connected with the history of medicine or pharmacy written by an undergraduate or graduate under the age of 30 on March 15, 1961. The first annual prize will be awarded for a historical essay of not more than 5,000 words on one of the following subjects: "The Relations Between Botany and Medicine"; or "The Relations Between Chemistry and Medicine"; or "The Relations Between Physics and Medicine." Those who wish to compete should send their names, before September 15, to Dr. F. N. L. POYNTER, the Honorary Secretary, The Wellcome Historical Medical Library, 183, Euston Road, London, N.W.1, from whom details may also be obtained. Completed essays must be submitted by March 15, 1961. The prize will be awarded at the Second Annual Students' Lecture in Apothecaries' Hall in June, 1961.

Horder Memorial Prizes

The British Spas Federation, of which the late Lord HORDER was president, is offering three prizes of £15 each for papers of original work relating to the medical and/or social problems of rehabilitation. Abstracts of such work should be submitted before the end of November to Professor R. E. TUNBRIDGE, Department of Medicine, the General Infirmary, Leeds, 1. Selected papers will be read at the annual general meeting of the Federation at Leamington on May 4, 1961, at which the prizewinners will be the Federation's guests.

Poisoning from Organo-phosphorus Compounds used in Agriculture and Horticulture

A note on these substances, which was prepared by a medical panel of the scientific subcommittee of the Advisory Committee on poisonous substances used in agriculture and food storage, was published in the *Journal* of July 16, p. 215. The following arrangements have been made to cover Scotland:

Supplier of P2S: Law Hospital, Carluke, Lanarkshire (Tel. Wishaw 621). *Blood Cholinesterase Estimation:* Estimations of the cholinesterase activity of blood samples can be carried out in the biochemistry laboratories of Edinburgh Royal Infirmary, Glasgow Royal Infirmary, Maryfield Hospital, Dundee, and Aberdeen Royal Infirmary.

Medical Publishers' Change of Ownership

The Practitioner Limited, a subsidiary of the Financial News Limited, has acquired the share capital of E. and S. Livingstone Limited, medical publishers, of Edinburgh. Lord DROGHEDA, Mr. MICHAEL FLETCHER, and Dr. W. A. R. THOMSON have been elected to the board. Mr. CHARLES MACMILLAN will continue as chairman and managing director of E. and S. Livingstone, and the management of the company will remain unchanged. (*The Times*, August 13.)

Mental Health

Copies of the principal regulations dealing with the exercise of compulsory powers in respect of persons liable to be detained in hospital or subject to guardianship under the *Mental Health Act, 1959*, are now available (H.M.S.O., 1960, No. 1241, *The Mental Health (Hospitals and Guardianship) Regulations*, 1960, price 1s. 3d. net).

Royal Society of Health

The Royal Society of Health announces that it has conferred Fellowships upon Dr. C. E. D. TAYLOR and Dr. D. K. MACTAGGART in recognition of their noteworthy public-health work.

Queen's Honorary Surgeon

Surgeon Captain J. A. SHEPHERD has been appointed an honorary surgeon to the Queen in succession to Surgeon Captain K. W. MARTIN.

Minister of Health's P.P.S.

The Minister of Health, Mr. J. ENOCH POWELL, has appointed Mr. MARCUS J. WORSLEY, M.P., to be his Parliamentary Private Secretary.

In Brief

Ten members of an expedition which is to study the effect of dehydration on the human body have left Algiers for three weeks in the Sahara. They are to be isolated in pairs, some not drinking at all, others drinking a range of specified amounts, and the rest existing on pills designed to slow down dehydration. (Reuter, *The Times*, August 8.)

People in the News

Sir JOHN CHARLES, chief medical officer of the United Kingdom, was chairman of the Fourth Expert Committee on Public Health Administration of W.H.O., which met in Geneva earlier this month to discuss the planning of public health services.

Dr. D. P. CUTHBERTSON, director of the Rowett Research Institute, has been elected an Honorary Member of the American Institute of Nutrition.

Dr. H. A. RUSK, director of the Institute of Physical Medicine and Rehabilitation of the New York University Medical Center, and associate editor of *The New York Times*, has been awarded the gold medal of the Hundred Year Association for his work in the field of medical rehabilitation.—(*New York Times*, July 23.)

Mr. A. H. R. ROWE, B.D.S., F.D.S., has recently been appointed part-time Dental Secretary of the Medical Defence Union.

COMING EVENTS

Royal Medical Benevolent Fund.—Annual general meeting, September 5, 5 p.m., at Medical Society of London, 11, Chandos Street, Cavendish Square, London, W.1. Tea from 4.30 p.m.

Society for Social Medicine.—St. Hugh's College, Oxford, September 29–October 1. Proceedings will include symposium, "Epidemiology of Leukaemia." Details from the Secretary, Society for Social Medicine, Department of Social Medicine, 8, Keble Road, Oxford.

Association of Clinical Biochemists.—Annual general meeting and scientific meeting, October 1, 9.30 a.m., at Royal College of Surgeons of England, held jointly with the Association of Clinical Pathologists and including symposium on "Malabsorption." Honorary Secretary: Dr. A. L. TARNOKY, Royal Berkshire Hospital, Reading.

10th Annual Instrument Symposium and Research Equipment Exhibit.—October 3–6 and October 4–7, respectively, at the National Institutes of Health, Bethesda, 14, Maryland, U.S.A. Details from Mr. J. B. DAVIS, at that address.

"Pathology and Treatment of Sexual Deviation."—As part of its contribution to World Mental Health Year, the Portman Clinic (formerly the psychiatric clinic of the Institute for the Scientific Treatment of Delinquency) is holding a two-day conference on October 11 and 12 on this subject (chairman: Dr. J. D. S. SUTHERLAND). Papers will deal with, among other aspects, the clinical approach in general psychiatry; the psychopathology and clinical treatment of male homosexuality; cultural differences in sexual deviation; and the pathology and treatment of sexual murderers. Details from Dr. ISMOND ROSEN, Portman Clinic, 8, Bourdon Street, Davies Street, London, W.1.

Society of Cardiological Technicians of Great Britain.—12th Annual Exhibition of Cardiological Apparatus, London Hotel, Welbeck Street, London, W.1. October 14 (5.30–8 p.m.), October 15 (9.30 a.m.–1 p.m.). Admission free by ticket. Apply to Cardiac Departments of St. Bartholomew's Hospital, London, E.C.1, or University College Hospital, Gower Street, London, W.C.1.

International Federation of Surgical Colleges.—Meeting at Royal College of Surgeons of England, London, October 18–20. Theme: "The Training of Surgeons." Programme will include lectures, research communications, and discussions. Those interested in attending all or part of meeting please write to the Secretary, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

R.A.F. Medical Branch Dinner.—Royal College of Surgeons, October 21. Details from Air Ministry (M.A.3), 1–6, Tavistock Square, London W.C.1.

Birmingham University.—Symposium, "Gastro-enterology," for consultants, S.H.M.O.s, and senior registrars, October 21 and 22. Details from the Secretary, Board of Graduate Studies, The Medical School, Birmingham, 15.

NEW ISSUES

ANNALS OF THE RHEUMATIC DISEASES

Gold Therapy in Rheumatoid Arthritis. Empire Rheumatism Council.
Gout in the Maori. G. A. Q. Lennane, B. S. Rose, and I. C. Isdale.
Renal Amyloid. R. H. Heptinstall and A. M. Jockes.
Fractures in Still's Disease. B. W. D. Badley and B. M. Ansell.
Haemophilia and Haemophilic Arthropathy. J. B. Webb and A. St. J. Dixon.
Arthritis and Rheumatism in the Insured Population of Northern Ireland. C. W. Kidd and A. T. Park.
On the Nature of the Rheumatoid Factor. F. Wöhler, W. Müller, and A. Hofmann.
Nail Studies in Rheumatoid Arthritis. E. B. D. Hamilton.
Articular Manifestations of Erythema Nodosum. L. H. Truelove.
Empire Rheumatism Council
Heberden Society
Notes
Abstracts

Volume 19, No. 2. (Quarterly; £3 annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday, August 24

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. Peter Clifford: Neoplasms of the Head and Neck in East Africa.

ROYAL FREE HOSPITAL, Gray's Inn Road, London, W.C.—5.15 p.m., Dr. Arnold S. Relman (Boston, Mass): Physiological Disturbances in Primary Aldosteronism.

Friday, August 26

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. Howard Nicholson.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—R. K. Dastoor, M.B., B.S., Orthopaedic Registrar, Norfolk and Norwich Hospital; J. J. Marian, F.R.C.S.C., M.R.C.S., L.R.C.P., Registrar in Thoracic Surgery, Regional Thoracic Surgery Unit, Papworth Hospital; H. K. El-Shamy, M.B., Ch.B., Registrar in Dermatology, North-west Area of Region; M. R. Pandey, M.B., B.S., M.R.C.P.Ed., D.T.M.&H., Medical Registrar, Newmarket General Hospital; Anthea M. Bushby, M.B., Ch.B., D.A., Anaesthetic Registrar, West Suffolk General Hospital; A. D. Broadhurst, M.B., Ch.B., Registrar in Psychiatry, Fulbourn and Addenbrooke's Hospitals; J. Watson-Farrar, M.B., B.Chir., F.R.C.S., Senior Registrar in Orthopaedic Surgery, United Ipswich Hospitals; Anne Ambrose, M.B., B.S., D.P.M., Senior Registrar in Mental Deficiency and Child Psychiatry, Little Plumstead Hospital Group and Child Psychiatry Service; D. G. A. Westbury, M.B., B.S., D.P.M., Senior Registrar in Psychiatry, Hellesdon Hospital, Norwich; G. A. Vassiliou, M.B., Registrar in Ophthalmology, Ipswich and East Suffolk Hospital, Ipswich; M. S. Luckhoo, M.B., Ch.B., Medical Registrar, North Cambridgeshire and Clarkson Hospitals, Wisbech; S. S. Ghatak, M.B., B.S., D.C.H., Medical Registrar, West Norfolk and King's Lynn General Hospital, King's Lynn; L. J. De Souza, M.B., B.S., F.R.C.S.Ed., Surgical Registrar, Peterborough Memorial Hospital.

MANCHESTER REGIONAL HOSPITAL BOARD.—H. F. McG. Bassett, M.B., B.S., F.R.C.S., Maximum Part-time Consultant Thoracic Surgeon, South Manchester and West Manchester Groups of Hospitals; T. L. Pilkington, M.R.C.S., L.R.C.P., D.P.M., Whole-time Consultant Psychiatrist and Medical Superintendent at Cranage Hall and Mary Dendy Hospitals, Cheshire; F. Hillman, M.B., B.Ch., M.R.C.P.I., D.Obst.R.C.O.G., Whole-time Consultant Pathologist, Wigan and Leigh Group of Hospitals; Catherine V. Longworth-Krafft, M.B., B.S., D.M.R.D., Consultant Radiologist (nine half-days weekly), Bolton and District Group of Hospitals; W. M. C. Allen, M.B., Ch.B., D.M.R.D., Consultant Radiologist (nine half-days weekly), North and Mid-Cheshire Group of Hospitals; J. R. Hutchinson, F.R.C.S.Ed., F.R.F.P.S., Consultant Traumatic and Orthopaedic Surgeon (nine half-days weekly), Burnley and District Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Carruthers.—On July 16, 1960, in hospital, Christopher Frank Johnstone Carruthers, M.B., Ch.B., of 184, Sands, Holmfirth, near Huddersfield, Yorks, aged 66.

Corbett.—On June 22, 1960, Catharine Louisa Corbett, M.B., Ch.B., D.P.H., of 1, Falcondale Road, Westbury-on-Trym, Bristol.

Doyle.—On July 15, 1960, at Sarratt, Herts, Martin Redfern Doyle, M.R.C.S., L.R.C.P.

Elder.—On June 29, 1960, in Aberdeen Royal Infirmary, James Elder, M.B., Ch.B., D.P.H., aged 76.

Gawn.—On July 14, 1960, at Glenhurst, Higher Downs Road, Babbacombe, Torquay, Devon, Ernest King Gawn, M.D., D.P.H., aged 87.

Gilchrist.—On July 8, 1960, at St. Mary's Hospital, London, W., Alexander Gordon Gilchrist, M.B., Ch.B., of 371, Hendon Way, London, N.W., late of Glasgow, aged 79.

Hanna.—On July 9, 1960, at the Royal Infirmary, Glasgow, John Hanna, M.B., Ch.B., of 7, Kilpatrick View, Dumbarton.

Hepworth.—On July 5, 1960, at Yeovil, Somerset, Sidney Milverton Hepworth, M.B., Ch.B., Colonel, I.M.S., retired.

Latimer.—On July 1, 1960, at North Cote, Ripon, Yorks, Janet Cameron Pearson Latimer (formerly Allison), M.B., Ch.B.

Phillips.—On July 10, 1960, in a nursing-home, Croydon, Surrey, Cyril Hamilton Phillips, M.D., of 76, Beechwood Road, Sanderstead, Surrey, late of Norbury, London, S.W., aged 87.

Sleigh.—On July 5, 1960, at Woodend Hospital, Aberdeen, George Baird Sleigh, M.B., Ch.B., aged 87.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Aetiology of Phobias

Q.—*What is the psychological explanation of isolated phobias in otherwise normal persons—e.g., a fear of nocturnal moths? Can such conditions be treated?*

A.—"The ideas of goblins and sprites have really no more to do with darkness than light; yet let but a foolish maid inculcate these often on the mind of a child and raise them there together, possibly he shall never be able to separate them again so long as he lives; but darkness shall ever afterwards bring with it those frightful ideas. . . ."

These words of Locke might equally have applied to moths, and little can be added to the understanding so clearly expressed in them. He even recognized the possible importance of a constitutional element in what has been called the normal or "universal" phobia.

Deconditioning treatment might be employed when the phobic situation can be reproduced. A domestic attempt at this in the case, for example, of mice could be made by keeping a few as pets and forcing oneself to endure contact with them until it ceased to be repellent. In the case of moths, butterflies might be kept in the manner of schoolboys, but the inconvenience of this might be thought greater than that of keeping the windows closed at night-time.

It is not likely that in a phobia of this kind psychotherapy would be at all helpful, since, as the questioner says, it may exist in a setting of complete normality in other respects. Thus there would be no psychopathology to deal with.

Herpes Labialis and Cardiac Ischaemia

Q.—*Is there any known association between herpes and ischaemic heart disease? A young man with marked labial herpes after an acute tonsillitis had an episode of constricting chest pain which lasted two hours. Serial E.C.G.s showed definite ischaemic changes.*

A.—So far as I am aware no association has been detected between herpes febrilis (labialis) and ischaemic heart disease. It is possible that an acute myocarditis might follow tonsillitis, especially if this was part of a generalized infection or other disturbance. However, constricting chest pain and cardiographic changes in a man 22 years of age are less likely to be due to ischaemic heart disease than to pericarditis or pulmonary embolism. So-called "benign" acute pericarditis is often preceded by an upper respiratory infection, and this might well be the cause in the case quoted. It is now realized that pulmonary embolism is more common than formerly suggested, and it can certainly cause chest pain and cardiographic changes. It is not possible to be more precise without further data on the clinical picture and the nature of the cardiographic changes in this case.

Polycystic Kidneys and Pregnancy

Q.—*A woman of 29 had a baby three years ago. She has been found to be suffering from polycystic kidneys, though in good health. Is a further pregnancy contra-indicated?*

A.—The advice to be offered to this patient depends on whether or not the condition is causing hypertension, reduced kidney function, or palpable renal enlargement. In the absence of these pregnancy should not influence the progress of the disease, but a careful watch for, and prompt and adequate treatment of, any urinary infection is very important. If there is hypertension but no impairment of renal function pre-eclampsia is likely to supervene by the 32nd–34th week of pregnancy, but careful management in hospital will probably result in the (induced) delivery of a premature but living baby. If renal function is seriously impaired, then, as in chronic nephritis, either the woman will not conceive or the pregnancy will abort. The reduced life-expectancy in this condition may also influence the patient and her husband on family size.

REFERENCE

1 Landesman, R., and Scherr, L., *Obstet. and Gynec.*, 1956, **8**, 673.

Mastalgia

Q.—*A woman aged 32 has complained of tender lumps in the left breast for more than two years—at first premenstrually and menstrually and now constantly. Treatment with testosterone, stilboestrol ointment, oral progesterone, and mild sedation has had no effect. There may be a little knottiness in the breast tissue, but it is not striking nor has it changed in two years. The patient is now seeking operation, but I do not agree with this. What advice do you give?*

A.—For this woman's peace of mind it would be best for her to be referred for the opinion of a surgeon, although from the information given operation is not likely to be advised. If no surgical lesion is found, further close questioning may elicit a psychic cause, for mastalgia, even if unilateral, may be due to underlying frustration, over-anxiety, or even cancerphobia. In such case reassurance can be given, a good supporting brassiere advised, and handling of the breast discouraged. Oestrogens are not indicated, for they may upset the menstrual cycle; progestogens (and androgens) are of value only when the mastalgia is part of a premenstrual tension state, in which event again uncovering of the basic worry is even better treatment.

Disinfecting Nail-brushes

Q.—*How may nail-brushes in a surgery be kept free from infection when a number of septic dressings have to be done in the course of the day? Is immersion in "dettol" or cetrimide sufficient, and, if so, in what strength? Do these antiseptics deteriorate on exposure to air?*

A.—The necessity for disinfecting nail-brushes can be reduced by using a germicidal soap containing hexachlorophane. The two disinfectants referred to do not lose strength by evaporation, but cetrimide is neutralized by soap, and both have a rather weak action on coliforms such as *Ps. pyocyanea*. A possibly better solution would be one containing sodium hypochlorite, mixed before use with a suitable detergent (some manufacturers of strong hypochlorite solutions also market detergents for use with them; they also issue instructions about concentrations required for different kinds of use). This is a good all-round germicide, and will keep a brush cleaner than any solution without similar surface-active properties. Brushes made of nylon withstand most chemical treatments better than those of natural bristle.

Bed-pan or Commode ?

Q.—*Should patients with recent myocardial infarction (first four weeks) be kept strictly in bed—that is, use a bed-pan only—or may they use a bedside commode?*

A.—In patients who are fit enough to use it the bedside commode probably causes less physical and certainly less emotional disturbance than the bed-pan, and therefore the commode should be used as soon as possible after the infarction if cardiac pain, high fever, hypotension, serious arrhythmia, and congestive heart failure are absent. Thus patients with minor infarctions may usually be allowed to use the bedside commode within a week of the acute episode and those with larger infarctions within two weeks, provided the above criteria have been satisfied. Rigid adherence to the bed-pan regime for weeks after an infarction enforces a degree of immobility which is physically and psychologically undesirable.

NOTES AND COMMENTS

Vitamin-E Therapy.—Dr. EVAN V. SHUTE (The Shute Institute, London, Canada) writes: Your issue of June 18 has just come to hand containing on p. 1905 the very misleading answer to a question on vitamin-E therapy. Tiresome as it is by this time, it seems the facts should once again be put forward. Vitamin E used therapeutically is rarely used for vitamin-E deficiency, but as a drug *per se*, much as vitamin K, or B_{12}, or niacin is used. It has certain unique and well-attested properties as an oxygen-conserving agent, a vasodilator, an anti-clotting agent, which everyone working in this field is aware of. Obviously such a safe and versatile agent must have value in treating cardiovascular cases, and about 300 groups of workers from a score of different countries have testified to that fact. One wonders how so many researchers could have been utterly mistaken. Did the physician who replied to this query see our exhibit of coloured photographs of results achieved with alpha-tocopherol shown at the combined British Medical Association and Canadian Medical Association meeting in Toronto in 1955 ? Has he seen the coloured photographs in our paper,[1] notably figures 1, 2, 3, and 10, 11, 12, and 13 ? I should also like to refer him to Kawahara.[2] I really feel that a man should be more aware of what has happened in alpha-tocopherol therapy in the last 14 years before he presumes to answer questions on it in your columns. In a day when cardiovascular morbidity and mortality continue to increase, despite a host of new drugs and operative procedures, it continues to amaze me that the simplest and best therapeutic measure, alpha-tocopherol, should not be used as generally and widely as it deserves to be. The next generation should look upon this as one of the medical curiosities of our time.

REFERENCES

1 Tolgyes, S., and Shute, E., *Canad. med. Ass. J.*, 1957, **76**, 730.
2 Kawahara, H., *Surgery*, 1959, **46**, 768.

OUR EXPERT replies: Dr. Shute is well known as an ardent advocate of vitamin-E therapy, but I am afraid that he and I must have wide differences of opinion about the standards for assessing the therapeutic potency of drugs. When he refers to vitamin K_1, or B_{12}, or niacin being used as drugs *per se* he seems to imply that these substances have therapeutic value in conditions other than those in which there is demonstrable deficiency of them in the body. I know of no convincing evidence that this is so. Although I was not present at the meeting in Toronto to which Dr. Shute refers, I am familiar with his many writings on the subject of vitamin-E therapy and I have read both the articles which he mentions. The results described therein are striking but are quite uncontrolled, and others have reported equally striking results in the treatment of cases of peripheral arterial disease with local gangrene without the use of vitamin E. It has been my personal experience and that of many others who have tried to repeat Dr. Shute's work that we have been unable to demonstrate convincingly that vitamin E has the dramatic effect that he claims for it in such cases. The fact that alpha-tocopherol is not generally and widely used does not amaze me; it merely confirms that the medical profession as a whole have not found it to be the simple and effective therapeutic measure which Dr. Shute would have us believe that it is.

Dr. L. SCHMIDT (Portland Place, W.1) writes: Having been away by health reasons I have read somewhat belatedly the answer of your expert to a question regarding vitamin-E therapy ("Any Questions ?" June 18, p. 1905). May I, as one who since 1948 has been carrying out clinical trials with this therapy fairly extensively and by publishing[1 2 3] the results of this treatment contributed in a small way to the "voluminous literature" which he so resentfully refers to, ask him: Did he really take the time and trouble to study seriously that literature ? It is difficult for me to believe that he has done so, otherwise he could have not so lightheartedly suggested that "there is no evidence to support the claim that vitamin E is of value in other forms of cardiovascular disease, such as coronary atherosclerosis." Just to the contrary, such a study would have enabled him to see that a great number of high-standing clinicians, pathologists, and biochemists—some of them world-wide reputation—on the basis of their studies are convinced that alpha-tocopherol can be and *is* a powerful therapeutic agent. Twelve years of my own clinical experience in a very substantial number of cases certainly fully corroborate this opinion. In my first publication[1] on this matter I gave *inter alia* the history of three cases of grave coronary thrombosis (one of them having been "given up" by the local specialist), each of which has not only fully recovered on proper vitamin-E treatment but, carrying on regularly with the latter during the following 12 years, had no further attack at all; yet it is general knowledge that the first attack of coronary thrombosis as a rule is a season ticket for the following ones. I am willing to show your expert the relative case histories and put him—if so desired—in personal touch with the patients in question.

REFERENCES

1 Schmidt, L., *Med. Wld (Lond.)*, 1950, **72**, 296.
2 —— *Lancet*, 1955, **2**, 1341.
3 —— *The Summary*, 1955, **7**, 64.

OUR EXPERT replies: Although I cannot claim to have read all the voluminous literature on the subject of vitamin-E therapy I can assure Dr. Schmidt that I have studied it seriously and critically and that I have some practical experience of the use of vitamin E in cardiovascular disease. He says "that a great number of high-standing clinicians, pathologists, and biochemists —some of them world-wide reputation—on the basis of their studies are convinced that alpha-tocopherol can be and *is* a powerful therapeutic agent," but he refers only to his own contributions on the subject. With two of these[1 2] I am familiar; the third[3] is in a Canadian medical journal which is not generally available in this country. From the evidence in these two communications I do not think that he can claim to have provided evidence which would satisfy a critically minded clinician that vitamin E is of value in coronary atherosclerosis. Any experienced physician is familiar with the apparently hopeless case of myocardial infarction in which the prognosis is confounded and the patient makes a remarkable recovery, even without vitamin E. It is well known that the severity of an acute attack of myocardial infarction is not always a guide to the eventual outcome.[4] Dr. Schmidt's statement that "it is general knowledge that the first attack of coronary thrombosis as a rule is a season ticket for the following ones" is not in accordance with facts. In the recent M.R.C. trial of long-term anticoagulant therapy following myocardial infarction the rate of reinfarction for males in the low-dosage (control) group was only 2.2 per 100 person months of exposure.[5] When he theorizes on the aetiology of coronary atherosclerosis from the results of the data from dietary surveys collected by others Dr. Schmidt[2] draws conclusions which are different from the interpretations made by those who collected the data and which have received considerable support from other experts in this field. Even if one accepts, as Dr. Schmidt postulates, that the low incidence of coronary atherosclerosis in certain races is due to the fact that they eat wholemeal bread it would still be far from proving that this was due to the presence of vitamin E in wholemeal bread. For example, an alternative hypothesis has been put forward by Sinclair,[6] who suggests that the high incidence of coronary atherosclerosis in the more highly civilized races is due to a deficiency of the essential polyethenoid fatty acids which are present in wheat germ but absent in low-extraction enriched flour.

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2 —— *Lancet*, 1955, **2**, 1341.
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4 Garai, O., and Smith, K. S., *Brit. med. J.*, 1958, **1**, 247.
5 Ibid., 1959, **1**, 803.
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